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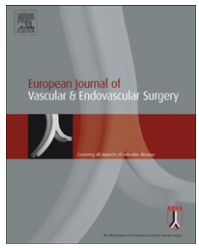

Use of B-Type Natriuretic Peptide to Predict Blood Pressure Improvement after Percutaneous Revascularisation for Renal Artery Stenosis

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Abstract *Objectives:* The purpose of this study was to evaluate the utility of B-type natriuretic peptide (BNP) to predict blood pressure (BP) response in patients with renal artery stenosis (RAS) after renal angioplasty and stenting (PTRA).
Methods: In 120 patients with RAS and hypertension referred for PTRA, 24-h ambulatory BP recordings were obtained before and 6 months after intervention. BNP was measured before, 1 day and 6 months after PTRA.
Results: BP improved in 54% of patients. Median BNP levels pre-intervention were 97 pg ml^{-1} (interquartile range (IQR) 35–250) and decreased significantly within 1 day of PTRA to 62 pg ml^{-1} (IQR 24–182) ($p < 0.001$), remaining at 75 pg ml^{-1} (IQR 31–190) at 6 months. The area under the receiver operating curve for pre-intervention BNP to predict BP improvement was 0.57 (95% confidence interval (CI) 0.46–0.67). Pre-intervention BNP >50 pg ml^{-1} was seen in 79% of patients with BP improvement compared with 56% in patients without improvement ($p = 0.01$). In a multivariate logistic regression analysis, BNP >50 pg ml^{-1} was significantly associated with BP improvement (odds ratio (OR) 4.0, 95% CI 1.2–13.2).

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Conclusions: BNP levels are elevated in patients with RAS and decrease after revascularisation. Although BNP does not seem useful as a continuous variable, pre-interventional BNP >50 pg ml^{-1} may be helpful to identify patients in whom PTRA will improve BP.

Renal artery stenosis (RAS) is an important cause of secondary arterial hypertension by means of inducing the renin–angiotensin system, volume expansion and sympathetic activation.[1] The use of renal angioplasty and stenting (PTRA) for RAS in patients with renovascular hypertension has become increasingly more common.[2] Despite high technical success and low restenosis rates, large observational studies and controlled trials have consistently shown that only about 60% of patients show improvement in BP after revascularisation of RAS.[3–5] The accurate prediction of achievable BP control, and therefore, selection of patients, which would undoubtedly benefit from revascularisation, is a major unmet clinical need.

B-type natriuretic peptide (BNP) may be an ideal biomarker to identify those patients who benefit the most from correction of RAS. BNP is a neurohormone synthesised and released predominantly from left and right ventricular myocytes in response to ventricular stretch in the setting of volume expansion or pressure overload and neurohormonal activation.[6] BNP is a well-established marker of congestive heart failure and the measurement of BNP is helpful in the emergency diagnosis of patients with acute dyspnoea.[7] Up-regulation of BNP has also been demonstrated in animal models and in patients with renovascular hypertension.[8,9] *In vitro* data suggest that Angiotensin II is able to induce BNP gene expression independent of myocardial stretch.[10] In a recent pilot study of selected patients with severe atherosclerotic RAS and refractory hypertension, referred for further treatment by means of renal artery revascularisation, BNP was shown to be useful in the prediction of BP response post-intervention.[11] The aim of this study was to evaluate the utility of BNP levels to predict BP response in unselected patients with significant RAS and arterial hypertension referred for PTRA.

Methods and Methods

Patient population

This prospective two-centre study included 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 $\geq$50% and arterial hypertension (systolic BP $\geq$140 mmHg and/or diastolic BP $\geq$90 mmHg or on any anti-hypertensive drug therapy). Assessment of RAS was based primarily on duplex ultrasound using a Philips ATL, HDI 5000 (Philips, Best, the Netherlands). As described previously, RAS was classified as haemodynamically relevant if the renal/aortal velocity ratio was $\geq$2.5.[12] For unilateral RAS, the side-to-side difference in intrarenal resistance index (RI = 1 − (end-diastolic velocity/peak systolic velocity)) between the two kidneys $>$0.05 was also used to classify haemodynamically relevant RAS. Before intervention, duplex ultrasound was always confirmed by intra-arterial angiography showing a percent diameter stenosis $\geq$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, translesional systolic pressure gradient of $\geq$20 mmHg was considered as haemodynamically relevant and was assessed in 31 patients.[12] A RAS $\geq$70% was documented in 87% of all patients and mean systolic pressure gradient was 72 $\pm$ 46 mmHg. Lesions were categorised as artherosclerotic or fibromuscular dysplasia.

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.

Revascularisation procedure

For atherosclerotic renal artery lesions, a stent placement procedure with and without predilatation 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). In patients with fibromuscular dysplasia, the lesion was dilated with an angioplasty balloon catheter without stent placement. Procedural success was defined as $<$30% residual luminal narrowing or residual peak translesional pressure gradient $<$10 mmHg. Anti-platelet 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 revascularisation procedure included duplex ultrasound with measurement of the renal/aortal velocity ratio and intrarenal RI, measurement of serum creatinine, 24-h ambulatory BP monitoring (BSI, SpaceLab Medical Inc., Issaquah, WA, USA) and documentation of anti-hypertensive drugs.

Two patients died during the follow-up period and five patients refused follow-up examination after PTRA (Fig. 1). Therefore, follow-up data regarding BP at 6 months were available from 120 patients (95%). Improvement in BP 6 months after PTRA was predefined as either clinical cure (systolic BP $<$140 mmHg and diastolic pressure $<$90 mmHg during 24-h BP monitoring, while receiving no anti-hypertensive medications) or clinical benefit in BP.[13] The criteria for a measurable clinical benefit included: (1) a decrease in mean arterial pressure of $\geq$5 mmHg on the same or reduced number of anti-hypertensive medications as before PTRA, or (2) no appreciable change in mean arterial pressure (decrease of less then 5 mmHg) and a reduction in one or

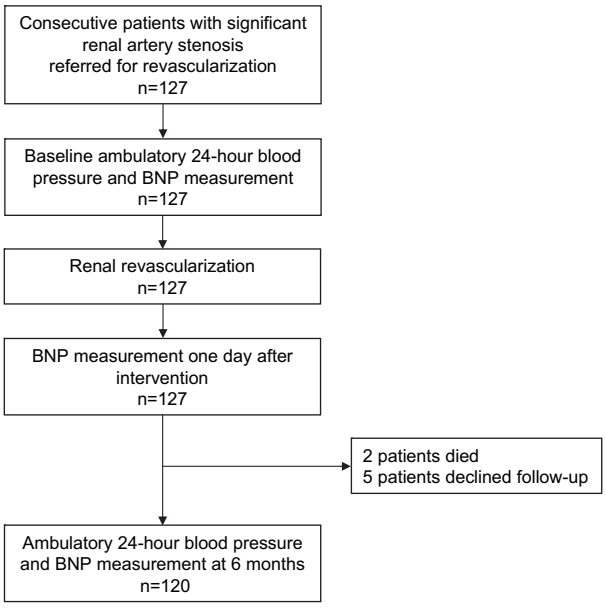

Figure 1 Flow diagram of patients with renal artery stenosis referred for revascularization.

more medications from baseline on mean 24-h BP. Clinical failure was defined as receiving no benefit from PTRA (that is, not fitting into any of the afore-mentioned classifications), as well as having to increase the number of antihypertensive medications from baseline, or finding an increase in mean arterial pressure at 6 months follow-up.

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 ethylene diamine tetraacetic acid (EDTA) and were centrifuged at 3000 *g* and analysed 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.[14] 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 1180.0 pg ml^{-1}, respectively. The analytic sensitivity was <5.0 pg ml^{-1}, with a measurable range of 0—5000 pg ml^{-1}. As previously described, age- and gender-specific median levels (25th and 75th percentiles) of plasma BNP using the same Biosite assay in 767 normal subjects in sinus rhythmus without cardiovascular disease or cardiac dysfunction were 27 (15, 43) pg ml^{-1} and 11 (5, 20) pg ml^{-1} for women and men of 55—64 years of age, and 29 (19, 52) pg ml^{-1} and 18 (7, 37) pg ml^{-1} for women and men of 65—74 years of age, respectively.[15]

The laboratory technician who measured BNP was blinded to patient information. To estimate the glomerular filtration rate (eGFR), we used the formula for creatinine clearance calculated by the abbreviated Modification of Diet in Renal Disease Study equation.[16]

Statistical analysis

The primary objective of this study was to examine whether pre-interventional BNP levels predicted improvement in BP by the 6 month follow-up end point.

Statistical analyses were performed using SPSS/PC (version 15.0, SPSS Inc., Chicago, IL, USA). Discrete variables were expressed as numbers and percentages, continuous variables as mean $\pm$ SD or median and interquartile range (25th to 75th percentiles) when the sample data was not normally distributed. Univariate analysis of patients with BP improvement compared to patients without BP 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. Area under the receiver operating characteristic curve was used to estimate the optimal cut-off of baseline BNP and decrease in BNP for the prediction of BP improvement. Multivariable logistic regression analyses were performed to assess the association of BP improvement with pre-intervention BNP >50 pg ml^{-1} (adjusted for age, sex, pre-intervention mean arterial pressure, eGFR <60 ml min^{-1} 1.73 m^{-2}, and intrarenal RI).

Results

Baseline characteristics and renal artery intervention

The baseline clinical characteristics are shown in Table 1. Haemodynamically relevant bilateral stenosis was found in 13 patients (11%). The majority of all lesions were atherosclerotic ostial stenoses (77%). RAS due to fibromuscular dysplasia was documented in 17 patients (14%). The primary technical success rates for renal revascularisation were 100%.

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

BP response

As shown in Table 1, mean systolic and diastolic BP decreased from baseline values of 148 $\pm$ 17 and 81 $\pm$ 13 mmHg before intervention to 137 $\pm$ 16 and 77 $\pm$ 11 mmHg after renal angioplasty at the 6 month follow-up ($p < 0.001$ for both). The number of anti-hypertensive agents significantly decreased from 2.9 $\pm$ 1.3 to 2.6 $\pm$ 1.4 ($p = 0.009$). BP improvement was documented in 54% of patients (65/120 patients). Three patients had a clinical cure of BP and 62 patients met the criteria for clinical benefit in BP. Differences in baseline characteristics between patients with and without BP improvement are

Table 1 Baseline characteristics of consecutive patients undergoing renal artery revascularization with and without blood pressure improvement during follow up.

	All patients ($n = 120$)	Patients with BP-improvement ($n = 65$)	Patients without BP-improvement ($n = 55$)	*P*-value
Age, y	63 ± 13	62 ± 14	65 ± 12	0.11
Male sex, *n* (%)	62 (52)	33 (51)	29(53)	0.83
Diabetes mellitus, *n* (%)	19 (16)	11 (17)	8 (15)	0.67
Hypercholesterolemia, *n* (%)	88 (73)	44 (68)	44 (80)	0.15
Smoker, *n* (%)	50 (42)	28 (43)	22 (40)	0.58
Co-morbidities:				
CAD, *n* (%)	44 (37)	25 (38)	19 (35)	0.62
PAD, *n* (%)	43 (36)	22 (34)	21 (38)	0.67
LVEF <40%, *n* (%)	6 (5)	3 (5)	3 (5)	0.89
Baseline eGFR, ml/min/1.73 m^2	66 ± 28	64 ± 31	67 ± 24	0.60
Follow-up eGFR, ml/min/1.73 m^2	69 ± 29†	69 ± 33†	68 ± 24	0.84
Basline eGFR < 60 ml/min/1.73 m^2, *n* (%)	52 (43)	32 (51)	20 (36)	0.11
Arterial hypertension:				
Refractory hypertension, *n* (%)	30 (25)	16 (25)	14 (25)	0.92
SBP at baseline, mmHg	148 ± 17	153 ± 16	141 ± 16	<0.001
DBP at baseline, mmHg	81 ± 13	84 ± 11	77 ± 14	0.003
MAP at baseline, mmHg	103 ± 13	107 ± 11	98 ± 13	<0.001
SBP at follow-up, mmHg	137 ± 16*	132 ± 15*	142 ± 17	0.002
DBP at follow-up, mmHg	77 ± 11*	74 ± 9*	79 ± 12	0.02
MAP at follow-up, mmHg	97 ± 11*	94 ± 9*	100 ± 13	0.005
Number of anti-hypertensive drugs at baseline	2.9 ± 1.3	2.8 ± 1.3	3.0 ± 1.3	0.38
ACE inhibitor or ARB at baseline, *n* (%)	80 (67)	43 (66)	37 (67)	0.91
Number of anti-hypertensive drugs at follow-up	2.6 ± 1.4†	2.2 ± 1.4*	3.0 ± 1.3	0.006
Renal anatomy and physiology:				
Kidney length, mm	103 ± 13	102 ± 12	104 ± 14	0.36
Renal/aortal ratio at baseline	5.2 ± 1.9	5.6 ± 1.9	4.9 ± 1.8	0.12
Intrarenal RI at baseline	0.63 ± 0.10	0.61 ± 0.10	0.64 ± 0.08	0.07
Bilateral stenosis, *n* (%)	13 (11)	9 (14)	4 (7)	0.25
≥70% stenosis, *n* (%)	104 (87)	59 (91)	45 (82)	0.15
Ostial stenosis, *n* (%)	92 (77)	46 (71)	46 (84)	0.06
Stent placed, *n* (%)	102 (85)	52 (80)	50 (91)	0.09
Fibromuscular dysplasia, *n* (%)	17 (14)	14 (22)	3 (5)	0.01

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; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; RI, resistive index. Data are expressed as mean ± SD, or number (percentage) of patients. *$P < 0.001$ compared with baseline, †$P < 0.05$ compared with baseline.

shown in Table 1. Factors significantly associated with BP improvement were elevated BP at baseline and fibromuscular dysplasia.

Angiographic imaging and clinical course of two typical cases are shown in Fig. 2.

BNP measurements in patients with and without BP improvement

Median BNP before revascularisation was 97 pg ml^{-1} (IQR 35—250) and decreased significantly within 1 day after PTRA to 62 pg ml^{-1} (IQR 24—182) ($p < 0.001$), remaining at 75 pg ml^{-1} (IQR 31—190) at the 6 month follow-up ($p = 0.02$ compared to pre-intervention). BNP levels at baseline, after revascularisation and 6 months' post procedure are shown in Table 2 and Fig. 3. To note, there was a trend towards increase in BNP from day 1—6 months after intervention in both groups in spite of sustained successful revascularisation of RAS.

The area under the receiver operating curve for the ability to predict BP improvement was 0.57 (95% confidence interval (CI) 0.46—0.67) for pre-intervention BNP and 0.56 (95% CI 0.45—0.87) for decrease in BNP 1 day after revascularisation. The most accurate cut-offs for pre-intervention BNP and decreases in BNP were 50 pg ml^{-1} and 20 pg ml^{-1}, respectively.

Pre-intervention BNP levels of >50 pg ml^{-1} were documented in 82 patients (68%) and were significantly associated with BP improvement (Table 2). In patients with BNP levels >50 pg ml^{-1}, BP improvement occurred in 62% of patients compared with 37% of patients with a pre-intervention BNP ≤50 pg ml^{-1} ($p = 0.01$) (Fig. 4). The sensitivity and specificity of using a pre-intervention BNP >50 pg ml^{-1}

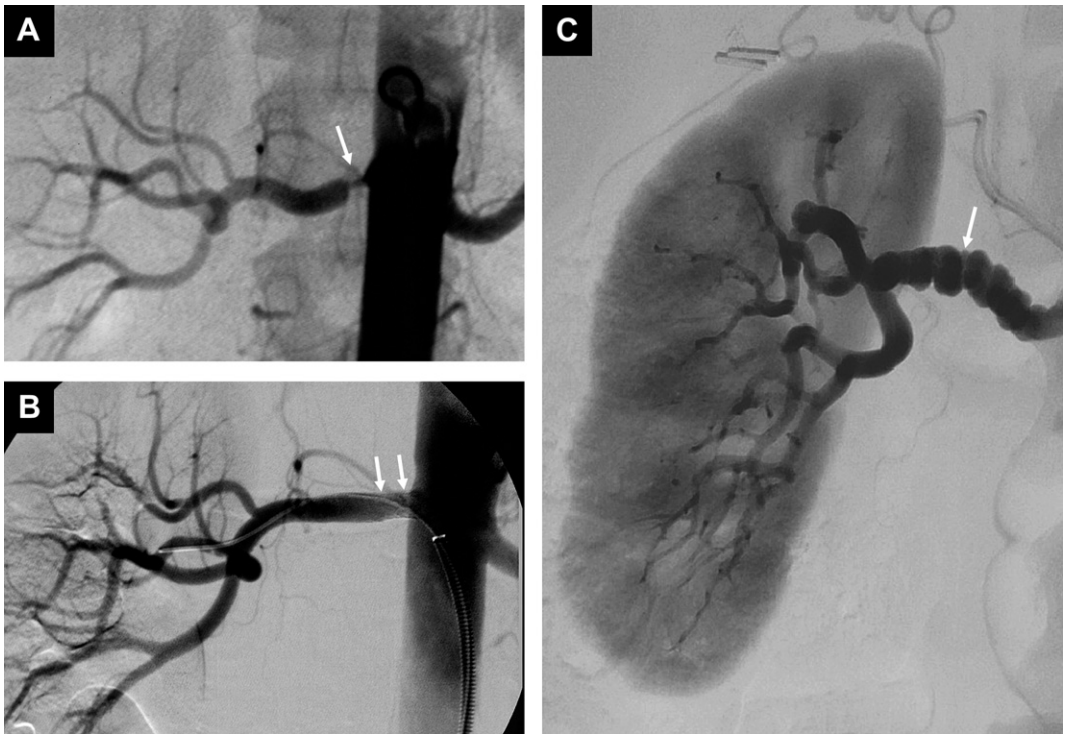

Figure 2 Angiographic imaging of renal artery stenosis in two typical cases. Panel A. Ostial atherosclerotic renal artery stenosis (arrow) in a 55-year old woman. The patient had blood pressure improvement (decrease in mean arterial pressure of 10 mmHg) six month after successful renal artery stent placement (panel B) (arrows). BNP level before revascularization was 80 pg/ml and decreased within one day of intervention to 50 pg/ml. Panel B. Renal artery fibromuscular dysplasia showing characteristic 'string-of-beads' appearance (arrow) in a 59-year old woman. The patient had blood pressure improvement (clinical cure) six month after angioplasty. BNP level before revascularization was 89 pg/ml and decreased within one day of intervention to 49 pg/ml.

Table 2 B-type natriuretic peptide levels in patients with and without blood pressure improvement during follow up.

BNP levels	All patients	Patients with BP-improvement	Patients without BP-improvement	*P*-value
Overall cohort	($n = 120$)	($n = 65$)	($n = 45$)	
BNP pre-intervention, pg/ml	97 (35, 250)	109 (53, 259)	68 (25, 237)	0.20
BNP >50 pg/ml pre-intervention, *n* (%)	82 (68)	51 (79)	31 (56)	0.01
BNP 1 day post-intervention, pg/ml	62 (24, 182)*	71 (21, 181)*	50 (24, 210)†	0.74
BNP decrease >20 pg/ml, *n* (%)	57 (47)	37 (59)	20 (39)	0.04
BNP 6 months post-intervention, pg/ml	75 (31, 190)†	89 (38, 191)†	63 (24, 199)	0.75
Patients with ≥70% atherosclerotic RAS	($n = 91$)	($n = 48$)	($n = 43$)	
BNP pre-intervention, pg/ml	109 (39, 265)	125 (55, 288)	95 (23, 237)	0.15
BNP >50 pg/ml pre-intervention, *n* (%)	65 (71)	40 (83)	25 (58)	0.008
BNP 1 day post-intervention, pg/ml	67 (24, 216)*	77 (31, 216)*	54 (24, 217)†	0.58
BNP decrease >20 pg/ml, *n* (%)	44 (48)	28 (58)	16 (37)	0.09
Patients with refractory hypertension	($n = 30$)	($n = 16$)	($n = 14$)	
BNP pre-intervention, pg/ml	119 (52, 305)	145 (73, 288)	59 (21, 405)	0.15
BNP >50 pg/ml pre-intervention, *n* (%)	23 (77)	16 (100)	7 (50)	0.001
BNP 1 day post-intervention, pg/ml	70 (34, 280)†	144 (41, 287)	54 (27, 290)	0.36
BNP decrease >20 pg/ml, *n* (%)	15 (50)	9 (56)	6 (43)	0.59

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

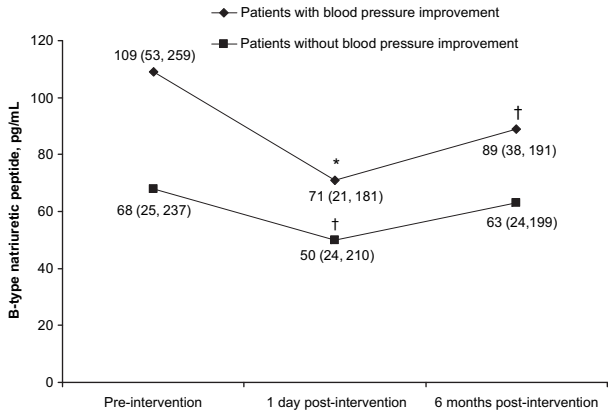

Figure 3 Median (25th to 75th percentiles) BNP levels before and after percutaneous revascularization for renal artery stenosis in patients with and without blood pressure improvement. *$P < 0.001$ compared to BNP levels pre-intervention, †$P < 0.05$ compared to BNP levels pre-intervention.

to predict BP improvement at the 6-month follow-up were 79% and 44%, respectively (Table 3).

A decrease in BNP >20 pg ml^{-1} 1 day after the intervention was revealed in 57 patients (47%) and was also significantly associated with BP improvement (Table 2). In patients with a decrease in BNP >20 pg ml^{-1}, BP improvement occurred in 65% of patients compared with 46% of patients with a decrease in BNP ≤20 pg ml^{-1} ($p = 0.04$) (Fig. 4).

As shown in Table 4, multivariate logistic regression analysis shows that elevated pre-intervention BNP levels >50 pg ml^{-1}, adjusted for age, sex, pre-interventional mean arterial pressure, eGFR < 60 ml^{-1} min^{-1} 1.73 m^{-2} and intrarenal RI, was significantly associated with BP improvement (odds ratio (OR) 4.0, 95% CI 1.2—13.2).

Subgroup analysis

After exclusion of patients with conditions other than RAS that might increase BNP, including congestive heart failure (left ventricular ejection fraction < 40%) and chronic renal insufficiency (elevated baseline creatinine ≥ 177 μmol l^{-1}) from the analysis, the diagnostic performance was similar. Sensitivity and specificity of using a pre-intervention BNP > 50 pg ml^{-1} to predict BP improvement in this subgroup were 75% and 48%, respectively. Higher diagnostic performance was found in 91 patients with ≥70% atherosclerotic RAS, and the highest sensitivity of 100% and a specificity of 50% were found in selected 30 patients with refractory hypertension (pre-interventional BP that could not be reduced to <140/90 mmHg with a three-drug regimen) (Table 3).

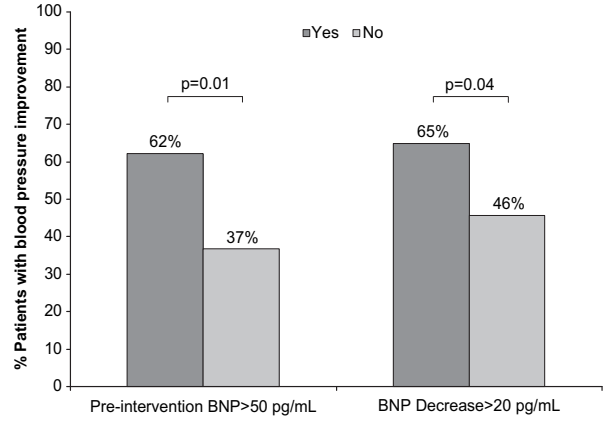

Figure 4 Percent of patients with blood pressure improvement 6 month after percutaneous revascularization for renal artery stenosis. Pre-intervention BNP >50 pg/ml vs pre-intervention BNP ≤50 pg/ml, and BNP decrease 1 day after intervention >20 pg/ml vs BNP decrease ≤20 pg/ml.

Discussion

This prospective study in unselected consecutive patients with haemodynamically relevant RAS and arterial hypertension referred for PTRA, evaluated the utility of BNP levels to predict BP improvement after successful revascularisation. One of the important strengths of our study design was that the BP response was quantified using 24-h ambulatory BP recordings. We report five major findings. First, pre-interventional BNP is elevated in most patients with RAS and decreases significantly 1 day after revascularisation supporting the pathophysiological concept that haemodynamically significant RAS causes elevations in BNP. Second, although BNP shows poor accuracy in the prediction of BP response when used as a continuous variable, in a multivariate analysis, BNP levels above 50 pg ml^{-1} before intervention was the strongest predictor and increased the chance of BP improvement at 6 months fourfold, independent of clinical and duplex sonographic parameters. In this analysis, prediction of BP response based on age and pre-interventional mean arterial pressure was less pronounced than BNP measurement. Thus, BNP measurement gives additional prognostic information and may improve prediction of treatment response currently based on clinical and Doppler sonographic (RI) variables. Third, in line with the concept that renovascular hypertension causes an elevation in BNP, we found that a decrease of BNP of more than 20 pg ml^{-1} 1 day after successful intervention was also significantly associated with BP improvement at the 6 month follow-up end point. Fourth, the highest sensitivity and negative predictive value when using pre-intervention BNP to predict BP improvement was found in selected patients with refractory hypertension. This observation confirms data from a recent pilot study by Silva et al.[11] Fifth, increased cardiac stress prevails even after successful correction of RAS in many patients. This phenomenon may be explained by persistent irreversible cardiac damage related to RAS or by cardiac disease independent of RAS. Moreover, BNP levels tend to increase again from day 1—6 months after revascularisation. These data suggest that some degree of progression of cardiac disease and cardiac stress prevails even after correction of RAS.

The BP response rate in our study was comparable to that observed in other large studies including unselected patients with reported cure of hypertension in less than 10% and improvement in 53%.[4] Therefore, achieving optimal clinical results for renal artery revascularisation is better predicated with a judicious patient selection. Multiple parameters have been evaluated for their utility in predicting which patients

Table 3 Diagnostic performance of BNP levels for the prediction of blood pressure improvement during follow up.

	Sensitivity	Specificity	NPP	PPV
Overall cohort ($n = 120$)				
BNP >50 pg/ml pre-intervention	79%	44%	63%	62%
BNP decrease >20 pg/ml	59%	61%	54%	65%
Patients with ≥70% atherosclerotic RAS ($n = 91$)				
BNP >50 pg/ml pre-intervention	83%	42%	69%	62%
BNP decrease >20 pg/ml	58%	66%	55%	64%
Patients with refractory hypertension ($n = 30$)				
BNP >50 pg/ml pre-intervention	100%	50%	100%	70%
BNP decrease >20 pg/ml	56%	54%	50%	60%

NPP indicates negative predictive value; PPV, positive predictive value; BNP, B-type natriuretic peptide; RAS, renal artery stenosis.

are most likely to benefit from PTRA in terms of BP control. Partly in line with our study, clinical parameters such as higher mean arterial BP at baseline, bilateral RAS, female sex, fibromuscular dysplasia and lower intrarenal RI in the segmental arteries measured by Doppler ultrasound have been associated with higher rates of improvement in BP in some but not all cohorts.[17–19]

Measurement of biomarkers, such as BNP, might improve patient selection for renal artery revascularisation. BNP is not only synthesised and released from left and right ventricular myocytes in response to ventricular stretch and neurohormonal activation, but is also released from glomerular mesangial and epithelial cells.[20] In the kidney, it increases glomerular filtration and inhibits sodium reabsorption, causing natriuresis and diuresis and promotes arterial and venous vasodilatation leading to reduced BP and ventricular preload.[6] Furthermore, BNP also has central and peripheral sympathoinhibitory effects, and it also inhibits the renin–angiotensin–aldosterone axis.[21] This regulation cascade incorporates several pathophysiological consequences of RAS.[1] Haemodynamically significant RAS leads to reduced renal perfusion and consequently to activation of the renin–angiotensin system mediated by angiotensinogen II, salt and water retention, and eventually to BP elevation. In addition, activation of the sympathetic nervous system may contribute also to hypertension in the setting of RAS.[22]

Our findings are in coherence with a recent pilot study in which BNP was investigated as a potential biomarker for renovascular hypertension in 27 selected patients with refractory hypertension and severe atherosclerotic RAS (≥70% diameter stenosis) referred for renal artery stent placement.[11] In this pilot study, using simple office BP measurements, BP improved in 63% of patients at 3.5 months of follow-up and median BNP level fell significantly 1 day after successful stent procedure. Elevated BNP >80 pg ml^{-1} at baseline and a pronounced decrease in post-treatment BNP correlated with improved BP control. Compared to a sensitivity of 79% and specificity of 44% in our study, elevated BNP before intervention was a stronger predictor of hypertension improvement at follow-up in their study (100% sensitivity, 50% specificity). Of note, in a subset of patients with refractory hypertension, we found the same sensitivity of 100% and specificity of 50%. As identical assays for BNP were used in our study and in the study by Silva and co-workers, the higher baseline BNP levels observed in their cohort (median 187 pg ml^{-1} vs. 97 pg ml^{-1} in our overall cohort and 119 pg ml^{-1} in patients with refractory hypertension) suggest further differences in baseline characteristics.[11] Furthermore, we demonstrate that applying BNP measurements to selected patients with atherosclerotic RAS ≥70% or refractory hypertension who benefit most from PTRA,[2,17] rather than unselected consecutive patients with hypertension and RAS, may pronounce BNP elevations and therefore, also the accuracy of using pre-intervention BNP to predict BP improvement. Hence, particularly in this subgroup of patients, BNP seems a new and interesting predictive marker of procedural success.

Furthermore, lower pre-interventional BNP levels in our study may explain the lower cut-off level of >50 pg ml^{-1} for predicting BP improvement. Cardiac structural diseases

Table 4 Multivariate analysis for the prediction of blood pressure improvement during follow up.

	Odds Ratio (95%CI)	*P*-value
Age	0.95 (0.89–0.99)	0.04
Male sex	0.6 (0.2–1.5)	0.23
MAP pre-intervention, mmHg	1.05 (1.01–1.20)	0.01
eGFR < 60 ml/min/1.73 m^2 pre-intervention	2.5 (0.8–7.2)	0.10
Intrarenal RI pre-intervention	0.52 (0.001–232.2)	0.83
BNP >50 pg/ml pre-intervention	4.0 (1.2–13.2)	0.02

BP indicates blood pressure; CI, confidence interval; MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide.

with consecutive BNP elevations are also prevalent in asymptomatic patients with essential arterial hypertension.[23] Therefore, aetiologies for BNP elevation other than renovascular hypertension may account for the low specificity found in both studies.[24]

Study limitations

Several limitations apply to this study. First, the exact onset of arterial hypertension was unknown in the majority of our patients. Therefore, we cannot examine whether the BP response rate, BNP levels and the accuracy of BNP to predict BP response is influenced by the duration of arterial hypertension. Second, in this prospective, non-randomised cohort study, all of the patients received percutaneous revascularisation of RAS without inclusion of any control group. Therefore, our results may not be applicable to patients undergoing surgical correction of RAS,[5] and we cannot preclude that factors other than RAS may have contributed to the elevation of BNP. However, median levels of BNP in our cohort with RAS were elevated compared with a previously published healthy control group and a patient cohort of severe essential hypertension.[9,15]

Conclusion

We found that BNP levels were elevated in unselected patients with hypertension and RAS referred for PTRA. BNP levels decrease significantly after successful revascularisation. Elevated pre-interventional BNP level >50 pg ml^{-1} and pronounced decrease of BNP >20 pg ml^{-1} 1 day after successful intervention was associated with 24-h ambulatory BP improvement at 6 months follow-up. Therefore, the use of pre-interventional BNP measurement may be helpful to identify patients with RAS in whom PTRA will improve BP. Further prospective interventional studies are needed to determine whether its use will lead to a more targeted use of PTRA.

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Conflict of Interest

Dr. Mueller has received research support from the Swiss National Science Foundation, Swiss Heart Foundation, the Novartis Foundation, Abbott, Biosite, Brahms, Roche, Siemens and the Department of Internal Medicine, University Hospital Basel, as well as speakers' honoraria from Abbott, Biosite, Brahms, Roche and Siemens. Dr. Zeller is member of the advisory board from SquareOne, Angioslide, Nemoscience and Avidal. He has received research support from Cook, Krauth Medical, Pathway Medical, Abbott Vascular, J&J Cordis, Angioslide, Ardian, Gore, Biotronik, Invatec, Lutonix, Spectranetics and ev3, as well as speakers' honoraria from Sanofi-Aventis, C.R. Bard, J&J Cordis, ev3, Boston Scientific, Straub Medical, Invatec, Biotronik, Optimed, Pathway Medical, Bracco, Medrad Possis, Abbott Vascular and Gore.

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