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Prognostic value of renal fractional flow reserve in blood pressure response after renal artery stenting (PREFER study)

Jacek Kądziela[1], Andrzej Januszewicz[1], Aleksander Prejbisz[1], Ilona Michałowska[1], Magdalena Januszewicz[2], Elżbieta Florczak[1], Łukasz Kalińczuk[1], Bożena Norwa-Otto[1], Ewa Warchoł[2], Adam Witkowski[1]

[1]Institute of Cardiology, Warsaw, Poland
[2]University of Medicine, Warsaw, Poland

Abstract

Background: *The aim of our study was to determine a potential relationship between resting translesional pressures ratio (Pd/Pa ratio), renal fractional flow reserve (rFFR) and blood pressure response after renal artery stenting.*

Methods: *Thirty five hypertensive patients (49% males, mean age 64 years) with at least 60% stenosis in angiography, underwent renal artery stenting. Translesional systolic pressure gradient (TSPG), Pd/Pa ratio (the ratio of mean distal to lesion and mean proximal pressures) and hyperemic rFFR — after intrarenal administration of papaverine — were measured before stent implantation. Ambulatory blood pressure measurements (ABPM) were recorded before the procedure and after 6 months. The ABPM results were presented as blood pressure changes in subgroups of patients with normal (≥ 0.9) vs. abnormal (< 0.9) Pd/Pa ratio and normal (≥ 0.8) vs. abnormal (< 0.8) rFFR.*

Results: *Median Pd/Pa ratio was 0.84 (interquartile range 0.79–0.91) and strongly correlated with TSPG ($r = –0.89$, $p < 0.001$), minimal lumen diameter (MLD; $r = 0.53$, $p < 0.005$) and diameter stenosis (DS; $r = –0.51$, $p < 0.005$). Median rFFR was 0.78 (0.72–0.82). Similarly, significant correlation between rFFR and TSPG ($r = –0.86$, $p < 0.0001$), as well as with MLD ($r = 0.50$, $p < 0.005$) and DS ($r = –0.51$, $p < 0.005$) was observed. Procedural success was obtained in all patients. Baseline Pd/Pa ratio and rFFR did not predict hypertension response after renal artery stenting. Median changes of 24-h systolic/diastolic blood pressure were comparable in patients with abnormal vs. normal Pd/Pa ratio (–4/–3 vs. 0/2 mm Hg; $p = NS$) and with abnormal vs. normal rFFR (–2/–1 vs. –2/–0.5 mm Hg, respectively).*

Conclusions: *Physiological assessment of renal artery stenosis using Pd/Pa ratio and papaverine-induced renal fractional flow reserve did not predict hypertension response after renal artery stenting.* (Cardiol J 2013; 20, 4: 418–422)

Key words: fractional flow reserve, renal artery stenting, pressures ratio

Address for correspondence: Jacek Kądziela, MD, PhD, Institute of Cardiology, ul. Alpejska 42, 04–628 Warszawa, Poland, tel: +48 22 343 42 72, fax: +48 22 613 38 19, e-mail: kadziela@ikard.pl

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Introduction

Atherosclerotic renal artery stenosis (RAS) is one of the common reasons for secondary hypertension [1–3] and increased risk of cardiovascular mortality [4, 5]. Despite excellent outcomes of renal artery stenting, clinical benefit from revascularization remains controversial [6]. Large randomized controlled trials comparing percutaneous angioplasty and optimal medical therapy did not prove revascularization advantages [7–12]. Thus, the identification of potential predictors for better long-term prognosis after renal stenting may improve appropriate selection of subjects for invasive treatment. During previous years several studies focused on physiological assessment of RAS with intrarenal pressure measurements. Both resting pressures ratio, called "Pd/Pa ratio", and hyperemic renal fractional flow reserve (rFFR), after papaverine or dopamine administration became helpful diagnostic tools [13–16]. First studies suggested also that translesional systolic pressure gradient and rFFR may predict the outcome after renal revascularization. The aim of our study was to determine a potential relationship between Pd/Pa ratio, rFFR and blood pressure (BP) response after renal artery stenting.

Methods

Study group

Out of 44 consecutive hypertensive patients with at least moderate unilateral RAS in noninvasive studies referred to renal angiography, 35 of them (49% males, mean age 64 years) with at least 60% stenosis in angiography, underwent renal artery stenting. Clinical examination was performed to determine demographics, duration of hypertension, cardiovascular risk factors, features of vascular disease and related comorbidities. Hypertension was diagnosed according to the World Health Organization (WHO) criteria (BP > 140/90 mm Hg or current antihypertensive treatment with at least 2 drugs). The number of antihypertensive drugs and drug daily doses according to WHO criteria [17] were recorded at baseline and at follow-up visit. Blood samples for all biochemical evaluations were taken after overnight fasting and after 60 min rest in supine position. Baseline serum creatinine was measured before the procedure, estimated glomerular fitration rate (GFR) was calculated using the MDRD formula [18]. Patients with severe valvular disease, NYHA III–IV heart failure and GFR below 30 mL/min, history of contrast nephropathy or refusal to provide informed consent were not included.

The study was approved by the Ethics Committee and signed inform consent was obtained from every patient.

Renal angiography

Renal angiography was performed using standard technique via femoral approach. Anterior-posterior, as well as 10–20° left oblique views were obtained. Quantitative analysis of stenosis severity was performed by an operator blinded to hemodynamic data. Minimal lumen diameter (MLD) was measured at the most tight lesion segment and compared to the reference lumen diameter (RLD) measured at the nearest normal (preferably proximal) artery segment. The percent diameter stenosis (DS) was calculated using the following formula: $DS = 1 - (MLD/RLD) \times 100$ [19].

Pressure measurements

Heparin (4000–5000 U) was administered to maintain adequate anticoagulation during the procedure. Renal distal pressure (Pd) was obtained using the 0.014'' Pressure Wire 5 (Radi Medical Systems, Sweden) advanced distally to the lesion, proximal pressure (Pa) was measured from the guiding catheter tip. During pressure measurements tip was disengaged from the artery ostium to avoid pressure damping. Resting Pd/Pa ratio was calculated as the ratio of mean distal to mean proximal pressures. Hyperemic rFFR was calculated in the same way after administration of 30 mg of papaverine. Papaverine was diluted in non-heparinized saline and given selectively into renal artery via 3 F multifunctional catheter advanced distally to the lesion (if possible) and quickly removed after drug administration. Non-ionic contrast agent and non-heparinized saline were used to avoid papaverine precipitation. Mean translesional systolic pressure gradient (TSPG) was counted as the difference between proximal and distal systolic pressure. In one case, very tight stenosis was not crossable with the pressure wire and required more stiff wire and predilation — this patient was not included in the analysis.

Procedure of renal stenting was successful if angiographic residual stenosis less than 20% was obtained.

Follow-up

Before the procedure and after 6 months renal duplex Doppler and computed tomography (CT) (for potential in-stent restenosis assessment)

were performed. Angio-CT examinations were performed with a 64-detector CT scanner (Somatom Sensation Cardiac 64; Siemens, Erlangen, Germany). For renal ultrasound, a HD11 (Philips, Eindhoven, the Netherlands) with a multiphase 2–4-MHz convex array transducer was used. None significant restenosis (> 50% of the vessel diameter) was detected.

Ambulatory BP measurements (ABPM) were recorded using a SpaceLabs 90207 or 90217 (Ambulatory Monitoring, Redmond, Washington, USA). Readings were obtained every 15 min during the day (6:00–22:00 h) and every 30 min during the night (22:00–6:00 h).

ABPM were performed before the procedure and after 6 months. One patient did not agree to have a follow-up visit. Patients were encouraged not to change their drug regimen during the follow--up period.

Statistical analysis

Continuous variables are presented as median and interquartile range. The mean deltas were assessed in Signed-Rank test and compared between subgroups using non-parametric Wilcoxon test with 2-tailed p value below 0.05 considered significant. R-Pearson correlations coefficient were estimated for categorical variables. Statistical analysis was performed using SAS V System ver.9.2.

Results

Characteristics of the studied group are depicted in Table 1.

Median Pd/Pa ratio was 0.84 (0.79–0.91) and strongly correlated with TSPG ($r = -0.89$, $p < 0.001$), MLD ($r = 0.53$, $p < 0.005$) and DS ($r = -0.51$, $p < 0.005$). No correlation was found between Pd/Pa ratio and GFR. After papaverine administration, proximal systolic pressure was reduced from 169 (158–187) to 153 (145–169) mm Hg, distal systolic pressure from 124 (110–147) to 103 (85–116) mm Hg, resulting in the increase of TSPG from 35 (23–52) mm Hg to 53 (46–65) mm Hg in maximal hyperemia.

The median rFFR was 0.78 (0.72–0.82) and was not associated with GFR. Similarly, significant correlation between rFFR and TSPG ($r = -0.86$, $p < 0.0001$), as well as with MLD ($r = 0.50$, $p < 0.005$) and DS ($r = -0.51$, $p < 0.005$) was observed.

Median 15 (12–18) mm of stent length under pressure of 12 (10–14) atmospheres was implanted. The stent length moderately correlated both with Pd/Pa ($r = -0.46$, $p < 0.01$), and rFFR ($r = -0.47$, $p < 0.01$). Angiographic procedural success was obtained in all patients. Median Pd/Pa ratio and rFFR after stent implantation were: 0.98 (0.95–1) and 0.98 (0.94–1), respectively. Before entering the study, patients were treated with 4.3 (2.6–6.9) defined daily doses of 3.5 (3–5) antihypertensive drugs.

Neither Pd/Pa ratio nor rFFR predicted hypertension response after renal stenting — the results of the ABPM are presented in Table 2. Only mild difference in daytime BP was observed between patients with Pd/Pa ratio below and above 0.9. However, it resulted from increased BP in patients with Pd/Pa ratio > 0.9, probably due to the changes

Table 1. Characteristics of the studied group. Data presented as median with interquartile range.

Age [years]	63.0 (53–72)
Males	48.6%
Diabetes mellitus	22.7%
Smoking: present/former	5.7%/48.6%
Hypercholesterolemia	82.9%
GFR [mL/min]	69.1 (61.1–85.1)
Diameter stenosis [%]	73 (66–80)
Minimal lumen diameter [mm]	1.5 (1.3–2.1)
Lesion length [mm]	12.5 (9.8–13.9)
TSPG at rest [mm Hg]	35 (23–52)
TSPG at max. hyperemia [mm Hg]	53 (46–65)
24 h ABPM systolic/diastolic blood pressure:	
Before procedure	136 (126–147)/ /71 (62–79)
After 6 months	135 (120–145)/ /69 (61–77)
Antihypertension treatment before procedure/after 6 months	
Number of drugs	3.5 (3–5)/3.4 (3–5)
Number of daily defined doses	4.3 (2.6–6.9)/ /4.1 (2.2–6.3)
Drug class taken at the study entry:	
ACEI/ARB	82%
Beta-blocker	89%
Calcium channel blocker	73%
Diuretic	66%
Alpha-1 adrenergic blocker	25%
Other	11%

GFR — glomerular filtration rate; TSPG — translesional systolic pressure gradient ABPM — ambulatory blood pressure; measurements ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin II receptor blocker

Table 2. Results of ambulatory blood pressure (BP) measurements in relation to baseline hemodynamic parameters. Data presented as median with interquartile range.

	Pd/Pa < 0.9	Pd/Pa ≥ 0.9	P	rFFR < 0.8	rFFR ≥ 0.8	P
Systolic BP						
Before intervention	137 (125–148)	135 (120–142)	NS	136 (122–149)	137.5 (129–144)	NS
After 6 months	135 (120–144)	136 (125–147)	NS	137 (120–146)	131 (119–143)	NS
p*	NS	NS		NS	NS	
Change:						
24 hours	–4 (–14–2.5)	0 (–4–15)	NS	–2 (–6–13)	–2 (–7–5.5)	NS
Daytime	–4 (–14–13.5)	9.5 (2–17)	< 0.05	3 (–11–17)	4 (–4–10)	NS
Night-time	–1 (–14–5)	–2 (–8–9)	NS	1 (–14–8)	–2 (–8–6)	NS
Diastolic BP						
Before intervention	71 (62–79)	72 (59–79)	NS	72 (63–79)	70 (58–77)	NS
After 6 months	68 (59–77)	74 (63–77)	NS	70 (61–85)	68 (61–75)	NS
p*	NS	NS		NS	NS	
Change:						
24 hours	–3 (–6.5–2.5)	2 (–2–5)	NS	–1 (–5–3)	–0.5 (–7.5–5)	NS
Daytime	–2.5 (–7.5–2.0)	3 (–2.5–10)	< 0.05	1 (–4–6)	1 (–6–3)	NS
Night-time	–3 (–7–3)	2 (–10–8)	NS	–3 (–7–4)	1 (–5–3)	NS

*p for difference in blood pressure between baseline and 6 months follow-up; Pd/Pa — renal artery pressures ratio (distal/proximal); rFFR — renal fractional flow reserve

in antihypertensive treatment during the follow-up period (–0.9 vs. 0.1 drug, $p < 0.05$).

Discussion

In our study, the relationship between hemodynamic parameters and BP response after renal artery stenting was not confirmed. Neither resting Pd/Pa ratio nor rFFR were related to ABPM changes after renal revascularization.

The utility of Pd/Pa ratio and rFFR as diagnostic tools in RAS assessment was demonstrated in only several trials [13–16]. Thus, the evaluation of its potential prognostic value in hypertension response after renal revascularization was urgently required. Previously published studies with rFFR or hyperemic systolic translesional gradient used only office BP measurements as the study endpoint [20, 21]. Since they have obvious limitations, trials with 24-h ABPM were expected. Our study is one of the first studies using ABPM in renal stenting evaluation in relation to hemodynamic measurements. First study using ABPM was published in December 2010 [22]. In this paper, in contrast to our results, the association between pressure gradients and BP improvement after renal stenting was observed. It is of note, that there are a few important differences between this study and reported by Mangiacapra et al. [22]. First of all, we used only papaverine bolus as hyperemic stimulus. 30 mg of papaverine as adequate dose in achieving of maximal hyperemia was previously proved [13]. Mangiacapra et al. [22] used not only papaverine but also dopamine in hyperemia inducement. And dopamine-induced, in contrast to papaverine-induced, mean gradient predicted hypertension response. Secondly, we calculated the baseline and hyperemic pressures ratios (called Pd/Pa and rFFR, respectively). In the study by Mangiacapra et al. [22] only mean hyperemic gradient (not ratio) was related to BP improvement. Thirdly, we performed slightly longer follow-up (6 vs. 3 months). And finally, our group had generally better pharmacologically controlled hypertension — mean systolic pressure obtained from ABPM was significantly lower than in the compared trial. That is probably the main reason why the overall benefit from revascularization was rather modest. The results are similar to ASTRAL study — the ever largest trial comparing medical therapy and revascularization — where renal stenting did not provide any additional benefit to standard medical therapy [11]. The ASTRAL study raised some doubts and criticism regarding the trial design — published elsewhere [23].

Limitations of the study

There are a few limitations to our study. Our group was relatively small — but one should take into account that recruitment to renal stenting

trials is very challenging. In ASTRAL study, the recruitment phase lasted 7 years and approximately 2 patients per year in each site were enrolled. After ASTRAL results presentation, number of revascularization procedures in patients with RAS significantly decreased. Our results represent the experience of 1 center, with 35 patients recruited. For comparison, previously published trials included from 13 to 61 patients. Thus, the results should be interpreted with caution.

Our group was quite heterogeneous with wide range of pre-procedure ABPM, that resulted from recruiting all consecutive patients referred to renal angioplasty. It might have had an influence on different BP response after revascularization and limited the value of obtained results.

Conclusions

Our study has found that physiological assessment of RAS based on papaverine-induced hyperemia does not predict BP response after renal artery stenting. Despite other trials, staying in contrast to our results, evaluating dopamine induced gradients and papaverine induced ratios, large multicenter trials with uniform methodology are still needed.

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Conflict of interest: none declared

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