

Comparison of early and late efficacy of percutaneous transluminal renal angioplasty with or without subsequent brachytherapy: The effect on blood pressure in patients with renovascular hypertension

Andrzej Lekston¹, Jerzy Chudek², Krzysztof Wilczek¹, Mariusz Gašior¹, Andrzej Więcek², Franciszek Kokot², Marek Fijałkowski³, Marek Gierlotka¹, Bożena Szyguła-Jurkiewicz¹, Roman Wojnicz¹, Brygida Białas³, Marcin Osuch¹, Bogusław Maciejewski³, Lech Poloński¹

¹3rd Department of Cardiology, Silesian Center for Heart Disease, Zabrze, Poland

²Department of Nephrology, Endocrinology and Metabolic Diseases, Silesian Medical University, Katowice, Poland

³Maria Curie-Skłodowska Center of Oncology, Gliwice Branch, Poland

Abstract

Background: Scarce data exist concerning the long-term effect of percutaneous transluminal renal angioplasty (PTRA) enhanced with intravascular gamma brachytherapy (IVBT) in patients with renovascular hypertension.

Methods: Seventy one patients aged 52 ± 8 years with refractory renovascular hypertension were randomized to Group I (PTRA + IVBT) or Group II (PTRA). For the IVBT procedure, the PARIS catheter and Microselectron HDR (Nucletron) system was employed. Both baseline and 9-month follow-up quantitative computerized angiography (QCA) and ambulatory blood pressure monitoring analysis was performed to assess luminal parameters of restenosis and the effect of treatment on blood pressure.

Results: Thirty three patients from Group I and 29 patients from Group II underwent successful procedure. During nine months of follow-up, three patients died; including two patients in Group I (cardiac causes) and one patient in Group II (stroke). The follow-up lumen diameter stenosis was $30.6 \pm 13.7\%$ and $40.4 \pm 11\%$ in Groups I and II, respectively ($p = 0.004$). Late lumen loss in quantitative computerized angiography was 1.2 ± 0.7 mm and 1.7 ± 0.7 mm in Groups I and II, respectively ($p = 0.004$).

Conclusions: Intravascular gamma brachytherapy using self-centering source performed after balloon angioplasty is a safe and effective method of prevention of restenosis after PTRA in patients with renovascular hypertension. (Cardiol J 2009; 16, 6: 514–520)

Key words: brachytherapy, renal artery stenosis, atherosclerosis, percutaneous transluminal renal angioplasty, hypertension

Address for correspondence: Andrzej Lekston, MD, PhD, 3rd Department of Cardiology, Silesian Center for Heart Disease, Szpitalna 2, 41–800 Zabrze, Poland, tel: +48 32 37 33 788; fax: +48 32 273 26 79; e-mail: scchs@sum.edu.pl

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Introduction

Among patients with potentially curable hypertension, the most common secondary cause of high blood pressure is renovascular hypertension due to renal artery stenosis, mostly of atherosclerotic origin [1–3]. Current data suggest that patients with renovascular hypertension of atherosclerotic origin may benefit from percutaneous revascularization, and the clinical benefits include blood pressure normalization or better blood pressure control, improved or stable renal function, and decreased requirement for antihypertensive drugs. Despite proven efficacy of angioplasty, especially with stent implantation, restenosis with its sequelae including worsening of blood pressure remains a significant problem, prompting attempts to decrease this risk. New methods of preventing restenosis that are currently under clinical investigation include drug-eluting stents and intravascular brachytherapy [4].

The aim of this study was to examine the effect of brachytherapy on limiting restenosis and blood pressure normalization as evaluated using ambulatory blood pressure monitoring (ABPM) during early and long-term follow-up after percutaneous transluminal renal angioplasty (PTRA) [5].

Methods

The study group included 71 consecutive patients aged more than 40 years with atherosclerotic renal artery stenosis accompanied by drug-resistant hypertension. The exclusion criteria included bleeding diathesis, thrombocytopenia, contrast agent intolerance, contraindications for the use of heparin, aspirin or clopidogrel, reference artery diameter of ≤ 3.0 mm, and stenosis localization unsuitable for PTRA. The study protocol was approved by a local Ethics Committee.

The diagnosis of renovascular hypertension of atherosclerotic origin was established or confirmed during hospitalization in the Department of Nephrology, Endocrinology and Metabolic Diseases, Silesian Medical University. PTRA procedures were performed in the Cardiac Catheterization Laboratory of the Silesian Center for Heart Disease, and intravascular gamma brachytherapy was performed in the Department of Brachytherapy, Maria Curie-Skłodowska Center of Oncology, Gliwice Branch, using PARIS® Catheter System self-centering sources.

The degree of renal artery stenosis was assessed using quantitative computerized angiography (QCA). Patients fulfilling the angiographic in-

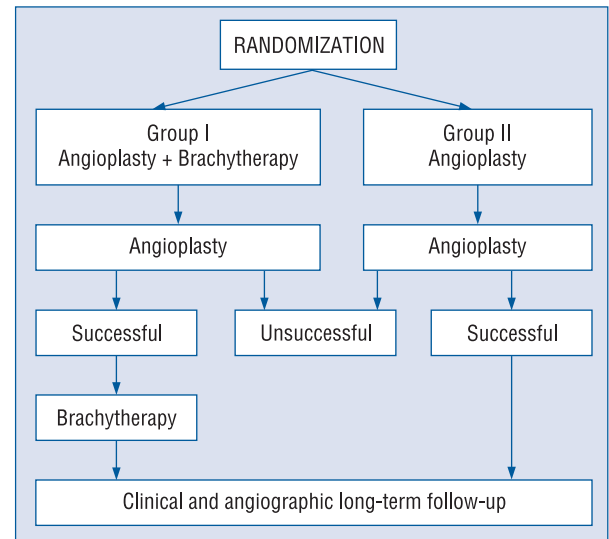


Figure 1. Study flowchart.

clusion criteria were randomized to one of the two groups using closed numbered envelopes (Fig. 1).

Two days prior to the PTRA procedure, patients were given 150 mg of acetylsalicylic acid and 300 mg of clopidogrel orally, and immediately before angioplasty 10,000 IU of heparin was administered intravenously. Previous antiplatelet therapy was also continued. According to the study protocol, a follow-up hospitalization at nine months was planned to perform a follow up renal angiography, intravascular ultrasound, and other noninvasive tests.

Angiographic criteria of a successful procedure

PTRA was considered successful if the residual lumen stenosis was less than 30%, partially successful if the residual lumen stenosis was 30–50% with its decrease by at least 15% compared to the baseline, and unsuccessful if the residual lumen stenosis was more than 50%, or its decrease compared to the baseline was less than 15%. During long-term follow-up, PTRA was considered successful if not accompanied by significant restenosis, with the latter defined as recurrent lumen stenosis of $\geq 50\%$ at the site of the previously treated lesion.

Invasive treatment efficacy based on the effect on blood pressure

Considering blood pressure values as the efficacy parameter [6, 7], the invasive treatment was considered:

- successful if postprocedural diastolic blood pressure was less than 90 mm Hg and/or decreased by at least 10 mm Hg;
- partially successful (associated with some improvement of blood pressure control) if postprocedural diastolic blood pressure was 90–110 mm Hg and decreased by at least 15% compared to the preprocedural blood pressure values;
- unsuccessful if postprocedural diastolic blood pressure exceeded 110 mm Hg and decreased by less than 15% compared to the preprocedural blood pressure values.

Angiography

Renal angiography and angioplasty was performed by femoral or radial approach, using 6 F to 8 F sheaths, wires and catheters. Measurements of renal arteries using QCA were performed on-line during the invasive procedures, and included preprocedural, postprocedural, and follow-up measurements. Both procedural and follow-up QCA measurements were also evaluated off-line by two blinded experienced invasive cardiologists.

Blood pressure evaluation

Blood pressure was measured by 24-hour ABPM before the procedure, at 48 hours after the procedure, and during long-term follow-up. Elevated blood pressure values were defined as systolic blood pressure above 140 mm Hg and diastolic blood pressure above 90 mm Hg during the daytime (6 am to 10 pm), and above 120 and 80 mm Hg, respectively, during the nighttime. Automatic blood pressure measurements were taken at 30 minutes intervals.

Intravascular brachytherapy

Intravascular brachytherapy was performed using the microSelectron HDR system (Nucletron) with iridium-192 source mounted on a self-centering PARIS catheter. Initial activity of the iridium-192 source was about 10 Ci. Reference isodose was 15 Gy at 2 mm from the surface of the centering balloon. Average duration of irradiation was 3 minutes (range 1.5 to 4.5 min). Average time interval between angioplasty and brachytherapy was 26 minutes. This delay, resulting from the need for patient transfer from the catheterization laboratory to the facility where gamma irradiation was performed, was minimized by establishing a special patient transfer system including dedicated ambulance.

Statistical analysis

Normally distributed parameters were presented as means \pm SD, and the differences between mean values were evaluated using the Student *t* test. Non-normally distributed variables were evaluated using the Mann-Whitney U test. Categorical parameters were evaluated using the χ^2 test with the Yates correction for expected size of less than 5. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the Statistica PL software, version 5.5 (StatSoft Inc.).

Results

The baseline clinical characteristics was similar in both groups. Overall, 71 patients (43 men and 28 women) were randomized and underwent PTRAs which was successful in 62 (87.3%) patients. In the remaining nine (12.7%) patients (males only), stents were implanted due to vessel dissection or only partial balloon dilatation of the lesion and these patients were excluded from the study as per protocol. No differences were found between baseline renal angiographic parameters in 33 patients randomized to PTRAs and brachytherapy (Group I) and 29 patients randomized to PTRAs only (Group II), in whom PTRAs were considered successful. No significant differences were seen in renal angiographic parameters between Groups I and II immediately following PTRAs. In contrast, long-term follow-up showed that the treatment was more effective in the brachytherapy group, as the late lumen loss in QCA was 1.16 ± 0.73 mm in Group I versus 1.71 ± 0.67 mm in Group II ($p = 0.0037$). Restenosis rate during long-term follow-up was 15.1% and 32.1% in Groups I and II, respectively ($p = 0.20$).

Blood pressure before and after the procedure

The mean 24-hour blood pressure before and after PTRAs was similar and did not differ significantly between the two groups (Table 1). In both groups, a significant decrease in systolic and diastolic blood pressure and blood pressure load was seen following the angioplasty (Table 1). Blood pressure normalization without the need for antihypertensive drug use was obtained in two (6%) patients in Group I and two (6.9%) patients in Group II. The proportion of patients with blood pressure lowering following the procedure was similar in both groups (21 [63.6%] patients in Group I vs. 19 [65.5%] patients in Group II). The treatment was unsuccessful in

Table 1. Blood pressure before and after the invasive treatment and at long-term follow-up.

	Before invasive treatment		P	After invasive treatment		P	Long-term follow-up		P
	PTRA + BR	PTRA		PTRA + BR	PTRA		PTRA + BR	PTRA	
Mean SBP	152 ± 7	152 ± 8	0.98	144 ± 8	143 ± 8	0.93	145 ± 8	148 ± 8	0.17
Proportion of elevated values	89 ± 10	89 ± 10	1.0	70 ± 14	68 ± 20	0.65	71 ± 15	78 ± 18	0.12
Mean DBP	108 ± 4	108 ± 5	0.76	91 ± 3	91 ± 4	0.48	93 ± 3	95 ± 5	0.05
Proportion of elevated values	96,6 ± 6	94 ± 9	0.37	65 ± 16	64 ± 16	0.76	65 ± 17	77 ± 18	0.01
Decrease in DBP*				17 ± 5	17.5 ± 5	0.84	15 ± 5	13 ± 6	0.05
Relative decrease in DBP (%)				15 ± 4	16.5 ± 5	0.61	14 ± 4	12 ± 5	0.05

PTRA — percutaneous transluminal renal angioplasty; BR — brachytherapy; SBP — systolic blood pressure; DBP — diastolic blood pressure; *postprocedural and long-term follow-up vs. baseline

regard to blood pressure lowering in ten (30.3%) patients in Group I and eight (27.6%) patients in Group II.

Blood pressure during the long-term follow-up

Three patients died during the follow-up, including 2/33 (6.1%) patients in Group I and 1/29 (3.4%) patients in Group II. The follow-up testing as per protocol was performed in the remaining 31 patients in Group I and 28 patients in Group II. During the long-term follow-up, normal blood pressure without the use of antihypertensive drugs was noted in 4/59 (6.8%) patients (two patients in each group). During this period, i.e. between PTRA and the follow-up testing, a significant increase in systolic and diastolic blood pressure was observed in both groups (Table 1). Systolic blood pressure values did not differ significantly between the two groups ($p = 0.17$), whereas diastolic blood pressure at the end of follow-up was significantly more reduced in Group I compared to Group II (15 ± 5 mm Hg *vs.* 13 ± 6 mm Hg; $p = 0.05$). In Group I, proportion of elevated blood pressure values after the procedure and at the final assessment was $70 \pm 14\%$ and $71 \pm 15\%$, respectively ($p = 0.56$), for the systolic pressure, and $65 \pm 16\%$ and $65 \pm 17\%$, respectively ($p = 0.33$), for the diastolic pressure. In contrast, proportion of elevated blood pressure values increased in Group II during the long-term follow-up both for the systolic pressure ($68 \pm 20\%$ after the procedure *vs.* $78 \pm 18\%$ at the final assessment $p \leq 0.001$) and the diastolic pressure ($64 \pm 16\%$ *vs.* $77 \pm 18\%$, respectively, $p \leq 0.001$). Overall, durable beneficial effect of the procedure in respect to blood pressure lowering was seen during the long-

-term follow-up in 17/31 (54.8%) patients in Group I and 10/28 (35.7%) patients in Group II.

At the final assessment, blood pressure response was successful or partially successful in 19/31 (61.3%) patients in Group I and in 12/28 (42.8%) patients in Group II. Invasive treatment was unsuccessful in 12 (38.7%) patients in Group I and in 16/28 (57.2%) patients in Group II. The latter patients required an increase in both number and doses of the antihypertensive drugs (Table 2). No association was seen between the degree of renal artery stenosis and blood pressure during the long-term follow-up, although a trend was noted ($p = 0.06$). In the present study, patients in both groups with improved blood pressure control had shorter duration of hypertension and were younger than patients with no improvement in blood pressure control (Table 3). In Group I, no significant difference was seen between the age of patients with improved blood pressure control and patients with no improvement in blood pressure control ($p = 0.2$), while duration of hypertension was significantly shorter in patients with improved blood pressure control compared to patients with no improvement in blood pressure control ($p = 0.05$). Both these differences were significant in Group II ($p = 0.008$ and $p = 0.02$, respectively), with patients with no improvement in blood pressure control being older and having longer duration of hypertension compared to patients with improved blood pressure control.

Discussion

Primary treatment goals in patients with renovascular hypertension include normalization or improved control of blood pressure, and improved

Table 2. Total daily dose of all antihypertensive drugs used before and after the invasive treatment and at long-term follow-up in the study groups (with a full dose of one drug counted as 1).

	Before	After	Long-term follow-up	P	P	P
	1	2	3	1 vs. 2	2 vs. 3	1 vs. 3
Dose (PTRA + brachytherapy)	3.2 ± 0.9	1.9 ± 1.1	2.1 ± 1.0	< 0.001	< 0.001	< 0.001
Dose (PTRA)	3.3 ± 0.9	2.0 ± 0.8	2.8 ± 1.3	< 0.001	< 0.001	0.050
P (PTRA + brachytherapy vs. PTRA)	0.63	0.66	0.038			

PTRA — percutaneous transluminal renal angioplasty

Table 3. Duration of the disease and age in relation to improvement of blood pressure control in the study groups.

	PTRA + brachytherapy			PTRA		
	Improvement	No improvement	P	Improvement	No improvement	P
Age	49.9 ± 6.6	54.1 ± 8.7	0.2	48.2 ± 6.4	55.9 ± 7.8	0.008
Disease duration	6.4 ± 3.2	9.6 ± 4.5	0.05	5.4 ± 3.3	8.5 ± 2.9	0.02

PTRA — percutaneous transluminal renal angioplasty

function of the ischemic kidney [8]. It should be noted, however, that not every successful renal angioplasty leads to normalization of blood pressure, and in some patients renal artery stenosis is not the major cause of hypertension. Published data differ widely in regard to the effect of renal angioplasty on blood pressure reduction and other clinical outcomes in patients with atherosclerotic renal artery stenosis [9–11]. In 1990 Ramsey et al. [7] performed a metaanalysis of 10 nonrandomized studies that showed limited efficacy of PTRA in the treatment of atherosclerotic renal artery stenosis, with outcomes similar to those in medically treated patients, and the proportion of patients with blood pressure normalization not exceeding 8%. Ascertainment of the real treatment effects is, however, difficult due to different patient selection criteria, various methods used to measure blood pressure, and varying criteria of improvement and cure. Among 190 patients with atherosclerotic renal artery stenosis, including 99 men and 91 women, who were treated by Bonelli et al. [12], successful blood pressure lowering defined as systolic blood pressure ≤ 140 mm Hg and diastolic blood pressure ≤ 90 mm Hg without the use of antihypertensive drugs was noted in only 8.4% of patients. The mean age in this patient subset, 58.6 years, was lower than among 70% of patients with only partial blood pressure response (64.8 years; p = 0.05). The authors noted that blood pressure normalization following

successful angioplasty in all patients with atherosclerotic renal artery stenosis is unlikely as coexisting essential hypertension might be present in most of these patients. Van Jaarsveld et al. [13] compared PTRA and medical treatment of renovascular hypertension in a randomized study in 106 patients. No significant differences of systolic and diastolic blood pressure were noted between the two groups at 3 months of follow-up. However, at 12 months blood pressure normalization without the use of antihypertensive drugs was seen in 7% (4/56) of patients compared to none of the patients in the medical treatment group, and improved blood pressure control in 68% (38/56) of patients compared to 38% (18/48) of patients treated medically. The choice of the invasive approach was also supported by the fact that 50% of patients in the medical treatment group were eventually treated with angioplasty due to inadequate blood pressure control and worsening of renal function. In a metaanalysis by Leertouwer et al. [14] in patient with atherosclerotic renal artery stenosis, blood pressure normalization without the use of antihypertensive drugs was noted in 10% (54/544) of patients undergoing PTRA, and somewhat lower proportion of patients cured by PTRA (8%) was reported by Klow et al. [15]. Better outcomes may be obtained by combining angioplasty with stenting, as blood pressure normalization without the use of antihypertensive drugs was noted in 11% (38/334) of such patients [8, 14].

Taking into account various criteria used in different studies, it has been estimated that in many centers the proportion of patients with blood pressure normalization without the use of antihypertensive drugs following PTRA ranges from 8 to 11% [7, 16]. The role of angioplasty compared to medical treatment in patient with renal artery stenosis has been further clarified by a metaanalysis of DRASTIC, SNRASCG, and EMMA studies [11, 17, 18] that was performed by Nordmann et al. [19]. These three studies included 210 patients with renal artery stenosis of $\geq 50\%$ and difficult-to-control hypertension. Overall, angioplasty without stenting was associated with reduced requirement for antihypertensive drugs and better blood pressure control (on average by 7/3 mm Hg compared to medical treatment), but the effect on renal function was comparable [11, 17, 18].

Our study showed that renal angioplasty combined with brachytherapy reduces the risk of restenosis during a 9-month follow-up by about 50% compared to balloon angioplasty only (32.1% vs. 16.1%). Our criteria of successful treatment in regard to blood pressure control were quite stringent, resulting in low proportion of hypertension cure at long-term follow-up (4/59 patients, i.e. 7%). Improvement of blood pressure control was seen in 54.8% of patients in the brachytherapy group and 35.7% of patients in the PTRA group. Most studies reported more beneficial effect of PTRA on blood pressure control and renal function compared to medical treatment. This was also reflected by a reduced number of antihypertensive drugs used after the invasive treatment [7]. Our findings regarding the number and doses of antihypertensive drugs in relation to blood pressure control before and after the invasive treatment and at long-term follow-up are fully concordant with the previous results.

Our findings showing a difference between the groups in the number of antihypertensive drugs used suggest that brachytherapy has a positive effect of renal artery patency and contributes to better blood pressure control during the long-term follow-up compared to angioplasty only. In addition, long-standing renal artery stenosis that is treated medically may lead to irreversible vascular structural changes, with increased stiffness of the vessel wall, as well as functional changes related to endothelial dysfunction. If these changes persist for a long time, even correction of the lesion by angioplasty, angioplasty with stenting, or angioplasty with brachytherapy, as in the present study, may not lead to durable normalization of blood pressure and renal function despite reversal of normal flow

in the renal artery [20]. Thus, blood pressure normalization following angioplasty is more likely in younger patients with shorter disease duration and a smaller likelihood of sustained changes in renal microcirculation [7, 16, 18, 20]. Our findings seem to support this view, although in our study age correlated with improvement in blood pressure parameters only in those patients who were not treated with brachytherapy ($p = 0.008$). In addition, in both groups duration of the disease was shorter in patients with improved blood pressure control following the invasive treatment.

In summary, the effectiveness of angioplasty in a broad population of patients with renal artery stenosis remains controversial. The key issue seems to be proper selection of patients who are most likely to benefit from the invasive treatment. This highlights the importance of appropriate diagnostic work-up and evaluation whether in a particular case medical treatment only is sufficient or should be supplanted by angioplasty [15]. Treatment decisions should be made on an individual basis, taking into account the previous course of the disease and the patient condition. It seems that medical treatment might be preferred over the invasive approach in the elderly patients who are both less likely to benefit from the intervention and are at higher risk of procedure-related complications.

Our findings in regard to blood pressure control support a significant effect of brachytherapy on the long-term efficacy of the invasive treatment of atherosclerotic renal artery stenosis. It remains, however, debatable, whether renal angioplasty should be considered as a treatment option in all patients with atherosclerotic renal artery stenosis. Clearly, screening all patients with hypertension for atherosclerotic renal artery stenosis with a prospect of angioplasty is not justified. On the other hand, renal angioplasty may be indicated in patients with atherosclerotic renal artery stenosis in whom blood pressure control remains inadequate despite the use of optimal antihypertensive drug regimen.

Conclusions

1. Complete blood pressure normalization without the use of antihypertensive drugs is a rare occurrence in patients with atherosclerotic renal artery stenosis despite successful angioplasty, but improved blood pressure control may be noted in many of these patients.
2. Angioplasty of renal artery stenosis leads to a decrease in systolic and diastolic blood pressure during hospital stay, but some subsequent

increase in blood pressure may be noted during long-term follow-up.

3. In patients undergoing brachytherapy, increase in diastolic blood pressure during long-term follow-up was significantly lower compared to patients who were treated only with PTR.
4. Improved vessel patency resulting from the use of brachytherapy attenuates the negative effect of longer duration of hypertension on improvement of blood pressure control during long-term follow-up.

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