Renal autoregulation in medical therapy of renovascular hypertension

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Abstract

Introduction: Renovascular hypertension (RVH) is caused by renal ischaemia associated with haemodynamically significant renal artery stenosis (RAS). The choice of optimal treatment of atherosclerotic RAS is still controversial. Increase in the renal resistive index (RI) value after captopril administration is considered to indicate preserved renal autoregulation. The objective of the study was to assess the effect of medical therapy of RVH on renal autoregulation efficiency in patients with atherosclerotic RAS.

Material and methods: 19 persons (38 kidneys) in 2 groups: 1) study: with RVH and stenosis of 1 renal artery – 8 patients; 2) control: – 11 healthy volunteers. Doppler captopril test with RI measurements and estimation of creatinine clearance (CCr) were performed in both groups at baseline, and after a period of controlled medical therapy (CMT) only in the study group. ABPM was evaluated in controls at baseline, and in the study group at the end of CMT.

Results: In the study group the mean period of CMT was 8.3 ±2.7 months, the number of antihypertensive drugs was 4.1 ±1.0, and mean 24-hour blood pressure was 138/74 mmHg. Mean CCr was stable during the study. Significant increase of RI after captopril was found only in controls. At baseline, in the group of kidneys with a non-stenotic renal artery, significant lowering of RI was observed, and ΔRI differed significantly from controls. After CMT, ΔRI increased in non-stenotic kidneys in comparison to the baseline, and did not differ from controls.

Conclusions: Adequate medical therapy of RVH preserved renal function and improved renal autoregulation efficiency in non-stenotic kidneys.

Key words: renal artery stenosis, renal resistive index, Doppler captopril test

Introduction

Renovascular hypertension (RVH) is caused by renal ischaemia related to haemodynamically significant renal artery stenosis (RAS). The most common causes of RAS are atherosclerosis, mainly in the elderly, and less frequently fibromuscular dysplasia of the renal artery, especially in young women. Renal artery stenosis occurs sometimes in the course of nodular arteritis, Takayasu disease or aortic dissection. The estimated incidence of renovascular hypertension (RVH) is 1-2% of the general population, about 5% of the population of all patients with arterial hypertension, and up to 40% of the population of patients with arterial hypertension and a history of RVH [1-3].

Through reduced renal blood flow, haemodynamically significant RAS leads to activation of the renin-angiotensin system and compensative

increase in blood pressure to improve perfusion of the ischaemic kidney [4]. On the other hand, initiation of compensative processes causes concomitant permanent, sometimes irreversible, damage of the contralateral kidney with a non-stenotic renal artery, manifested, for example, by higher values of vascular resistance and lower glomerular filtration rate independent of reperfusion as compared to kidneys with a stenosed artery [5, 6].

Many reports relating to the efficacy and methods of treatment of atherosclerotic RAS are inconsistent [7-10]. From an aetiological point of view it seems that it is best to perform angioplasty with stenting. However, not all patients benefit from invasive treatment and 5-year survival rates do not significantly differ between patients treated invasively and conservatively.

The renal resistive index is an accepted marker of vascular-interstitial damage to the kidneys, constituting a predictive factor for delayed effects of invasive treatment of RAS [11]. However, its value depends on such parameters as age, blood pressure level and arterial stiffness. Therefore, the diagnostic usefulness of RI is higher in repeatable measurements such as the Doppler captopril test or in compared measurements between both kidneys as taken in the diagnosis of renal artery stenosis. The measurement of variability of the renal resistive index before and after captopril administration is a non-invasive method of assessment of renal autoregulation efficiency. A positive value of ΔRI expresses preserved renal autoregulation [12-14].

The study objective was to assess the effect of controlled medical therapy of renovascular hypertension on renal autoregulation efficiency and renal function.

Material and methods

Nineteen persons (38 kidneys) were enrolled in the study and divided into 2 groups: 1) the study group with hypertension and stenosis of 1 renal artery confirmed by spiral computed tomography, consisting of 8 patients (2M + 6F); 2) the control group – 11 healthy volunteers (6M + 5F). Baseline characteristics of studied groups are shown in Table I. Patients were recruited from consecutive subjects who had been admitted to the Nephrology Department over a 1-year period.

Exclusion criteria included: renal insufficiency with serum creatinine levels > 3 mg/dl, glomerular, tubulointerstitial and obstructive renal diseases, liver failure, diabetes, intolerance of or allergy to angiotensin-converting enzyme inhibitors, and ongoing treatment with non-steroidal anti-inflammatory drugs. The study was conducted before (baseline) and after about 6 months (Figure 1) of

Table I. Baseline characteristics of studied groups

	Controls (n = 11)	Study group (n = 8)	p-value
Age [years]	34.4 ±12.7	56.4 ±12.7	< 0.05
BMI (kg/m^2)	23.8 ±3.8	26.4 ±2.7	NS
Smoking habit [years]	0.0	18.4 ±13.9	< 0.001
EH duration [years]	0.0	15.1 ±11.4	<0.001
LDL(s) [mg/dl]	97.8 ±20.9	137.6 ±42.3	<0.05
Creatinine(s) [mg/dl]	0.85 ±0.16	1.19 ±0.66	NS
UAER [g/24 hrs]	13.3 ±8.7	10.5 (3.0-2960.0)	NS
RAS [%]	–	55.6 ±14.0	–

UAER – urinary albumin excretion rate, RAS – renal artery stenosis, (s) – serum, NS – non-significant

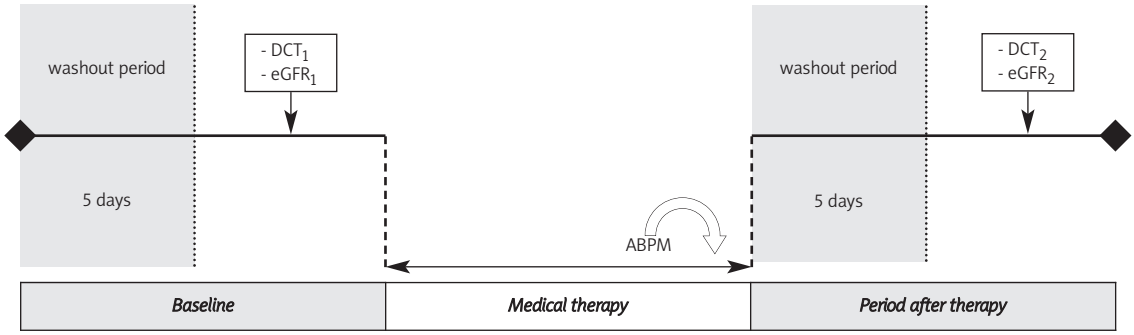

Figure 1. Study protocol diagram

controlled medical therapy (CMT). Modification of antihypertensive treatment during CMT is shown in Table II.

The tests included the Doppler captopril test (DCT) for each kidney and estimation of creatinine clearance (CCr) by the Cockcroft-Gault formula. The tests were performed after a 5-day washout period of withdrawal of antihypertensive drugs, except β-blockers if they were used. Ambulatory blood pressure monitoring (ABPM) was performed at baseline in the control group and at the end of the period of controlled medical therapy in the study group.

The renal resistive index (RI) was assessed by Doppler ultrasonography (GE LOGIQ 400, convex transducer 3.5-5 MHz) in segmental and interlobar arteries of the kidneys, using the Pourcelot equation, as the ratio of the difference between maximum systolic velocity (Vs) and end-diastolic velocity (Vd) to the maximum systolic velocity: RI = (Vs–Vd)/Vs. RI for each kidney was a mean of 3–5 measurements performed in various regions of the renal sinus. The Doppler spectrum was captured after an angle correction of ≤ 60° to the vessel axis.

The Doppler captopril test protocol was described previously [15]. It involves RI measurement before (Phase 0; RI_0) and 60 minutes after oral administration of captopril 50 mg (Phase 1; RI_1), with blood pressure measurement on the brachial artery performed each time (Figure 2) [12, 16, 17]. Renal autoregulation efficiency was calculated as the change of the renal resistive index (ΔRI) in the Doppler captopril test, using the formula: $\Delta RI = 100^*(RI_1–RI_0)/RI_0$ [18].

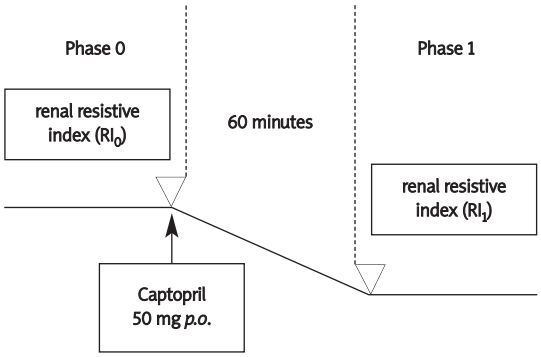

Figure 2. Doppler captopril test diagram

The local bioethics committee approved the protocol of the study. All participants enrolled in the study gave informed consent.

Statistical analysis

Patient and kidney-level analyses were performed. The examined variables were analysed with Student's *t*-test, Wilcoxon or Mann-Whitney test, as determined by meeting the condition of normal distribution, and by correlation between the analysed variables.

Results

All patients and controls positively completed tests. The mean duration of CMT was 8.3 ±2.7 months. All patients were treated with an angiotensin-converting enzyme inhibitor and a calcium channel blocker as well as other available antihypertensive drugs. The mean number of antihypertensive drugs was slightly higher in CMT in comparison to the baseline (4.1 ±1.0 vs. 3.8 ±1.1, $p = 0.07$). ABPM was performed in all persons in the control group at baseline and in 6 patients in the study group at the end of controlled medical therapy. Results of ABPM in controls and in the study group are presented in Table III. For ethical reasons, only baseline tests were performed in the control group.

Table IV presents a comparison of the DCT results at baseline and after CMT between the control and study groups in stenotic and contralateral kidneys.

In all study subjects, captopril administration caused a significant reduction of systolic and diastolic blood pressure ($p < 0.05$). A significant

Table II. Modification of antihypertensive treatment

Number of drugs per patient	Baseline ($n = 8$)		CMT ($n = 8$)	
	n	treatment	*n*	treatment
3	4	(1x CCB+ACE-I+D) (1x CCB+ACE-I+BB) (1x CCB+D+BB) (1x CCB+D+CN)	2	(1x CCB+ACE-I+D) (1x CCB+ACE-I+BB)
4	2	(2x CCB+ACE-I+BB+D)	4	(3x CCB+ACE-I+D+BB) (1x CCB+ACE-I+D+CN)
5	1	(CCB+ACE-I+D+BB+A)	1	(CCB+ACE-I+D+BB+A)
6	1	(CCB+ACE-I+BB+T+A+CN)	1	(CCB+ACE-I+BB+D+T+CN)

BB – beta blocker, CCB – calcium channel blocker, ACE-I – inhibitor of angiotensin-converting enzyme, T – thiazide diuretic, D – loop diuretic, A – aldosterone blocker, CN – centrally acting drug

increase in RI after captopril was found only in the control group. In contralateral kidneys with a non-stenotic artery, a significant lowering of RI was observed in baseline evaluation but not after CMT. In kidneys supplied by a stenotic artery RI did not change significantly in DCT at both stages. A comparison of renal autoregulation efficiency showed a significant increase in ΔRI in the group of kidneys with a non-stenotic renal artery after CMT – this value did not differ from ΔRI in the control group (Figure 3).

Renal function parameters did not change significantly during the observation (Table V).

Discussion

So far, no consistent guidelines have been developed on the best method of treatment of renovascular hypertension [7, 9]. In randomised studies, benefits such as improved renal function were obtained by about one-fourth of patients treated with angioplasty with stenting, in half of them no differences were found, and in the remaining ones organ function impairment was found [9]. However, in most patients treated invasively, a significant reduction in the number of antihypertensive drugs is possible [19]. The cause of this is attributed to poor selection of patients eligible for angioplasty, overestimation of stenosis grade by angiography, as well as accompanying renal parenchymal injury [9]. It is suggested that patients with marked (> 70%) stenosis of one renal artery or stenosis of both renal arteries or stenosis of the renal artery of a single functional kidney should be found eligible for invasive treatment. Less significant stenosis should be dilated if is accompanied by clinical symptoms such as persistent hypertension, congestive heart failure, sudden pulmonary oedema, reduced size of the kidney with stenosed artery, or rapid progression of renal insufficiency, especially after the use of angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin AT_1 receptor blockers (ARB). In the remaining cases, invasive treatment is questionable. In our study, patients with RVH had relatively good control of blood pressure (RR 138/74 mmHg).

Table III. Diurnal blood pressure in studied groups

Variable	Control group (baseline) (n = 11)	Study group (end of CMT) (n = 6)	p
SBP [mmHg]	117.5 ±8.3	137.7 ±20.1	0.035
DBP [mmHg]	69.9 ±5.3	74.2 ±10.0	NS
MAP [mmHg]	85.8 ±5.7	95.2 ±12.8	0.052
PP [mmHg]	47.6 ±6.7	64.2 ±13.5	0.004

CMT – controlled medical therapy, NS – non-significant

Mean degree of renal artery stenosis was 56%, without coexistence of clinical indications for revascularization.

In our study, we assessed the effect of 8-month medical therapy on renal autoregulation efficiency in patients with stenosis of a single renal artery. An increase of the RI value in the captopril test was significant only in the group of healthy persons. In both study stages, a positive value of ΔRI was not obtained or the increase of RI after captopril was not significant in the study group, which suggests impaired renal autoregulation. Similar observations were made by Veglio *et al.* in a group of 45 patients with essential hypertension and a group of 15 healthy persons. In this study, a significant increase of RI after captopril administration was obtained only in healthy persons and in patients with signs of mild hypertension. In patients with

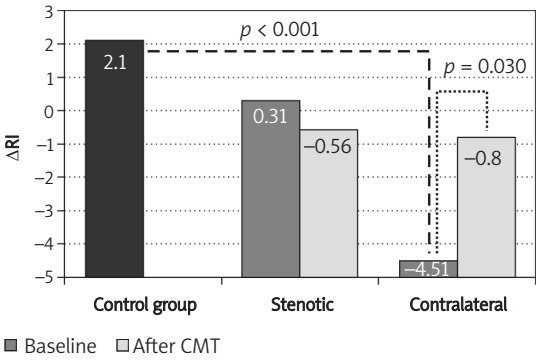

Figure 3. Variability of ΔRI in studied groups

Table IV. Comparison of DCT scores for stenotic and contralateral kidneys

Group/period	RI		ΔRI [%]	p-value (Phase 0 : 1)
	Phase 0	Phase 1		
Control (n = 11)	0.603 ±0.049	0.616 ±0.054	2.10 ±1.87	< 0.004
Contralateral/baseline (n = 8)	0.748(**) ±0.071	0.709(*) ±0.072	m. –4.51(**) (–11.62 : –0.27)	< 0.01
Contralateral/after CMT (n = 8)	0.724(**) ±0.076	0.719(*) ±0.067	m. –0.08(^{S}) (–5.80 : 7.37)	NS
Stenotic/baseline (n = 8)	0.695(*) ±0.073	0.695(*) ±0.091	m. 0,31 (–9.32 : 7.43)	NS
Stenotic/after CMT (n = 8)	0.663 ±0.129	0.674 ±0.093	m. –0.56 (–11.6 : 50.7)	NS

CMT – controlled medical therapy period. Significance level versus the control group: (*) for $p < 0.05$; (**) for $p < 0.001$. (^{S}) for $p = (0.05\text{-}0.1)$. NS – non-significant, $\Delta RI\ (\%) = 100^*(RI_1–RI_0)/RI_0$

Table V. Comparison of kidney function in study and control groups

Variable	Period	Control group (n = 11)	Study group (n = 8)	p-value vs. control group (p)
Creatinine [mg/dl]	I	0.85 ±0.16	1.19 ±0.66	NS
	II	–	1.30 ±1.22	NS
	p (I : II)	–	NS	–
Creatinine clearance [ml/min]	I	116.4 ±21.4	68.5 ±7.94	< 0.001
	II	–	75.6 ±24.9	0.001
	p (I : II)	–	NS	–

Period I – baseline, Period II – after controlled medical therapy, NS – non-significant

more advanced hypertension the RI change was insignificant [13]. In another study, Veglio *et al.* found significant lowering of the renal resistive index after captopril administration in kidneys with a stenosed artery, while in kidneys with a normal artery an increase of RI was found [12]. In our study, the higher baseline values of RI in kidneys with a non-stenotic renal artery and significant reduction of RI in DCT suggest more important vascular-interstitial damage of kidneys with a normal artery, which may explain the difference between our results and the observations of Veglio *et al.* After 8 months of medical therapy, pre-captopril RI values were bilaterally slightly lower than before treatment, and captopril administration caused a smaller reduction of the renal resistive index. These changes applied especially to kidneys contralateral to stenosis, with a normal artery. ΔRI was significantly lower at baseline in kidneys with a non-stenotic artery but did not differ significantly from the control group after CMT, although it was still negative. This reflects an improvement but still not normalisation of autoregulation in this group of kidneys. Assessing separated renal clearances before and 12 months after initiation of treatment in the group of 46 patients with renal artery stenosis > 70% treated by angioplasty with stenting (n = 27) and conservatively (n = 19), Coen *et al.* found a significant improvement in function of kidneys with a stenosed artery, in contrast to a significant impairment of function of kidneys with a non-stenotic artery [6]. Total renal function did not significantly change, both in the group treated invasively as well as in the group treated conservatively. On the other hand, Wheatley *et al.* (The ASTRAL Investigators) in two groups of 403 patients with RAS, receiving medical therapy alone or with revascularization, did not find any significant differences in progression of renal impairment, systolic blood pressure, major cardiovascular event, or death [20]. With respect to stability of renal function, the results of our study do not differ from observations made by the ASTRAL Investigators and Coen *et al.* However, bilaterally lower pre-captopril RI values after drug therapy and lower amplitude of negative ΔRI values in contralateral kidneys suggest reduction of organ damage and improvement of renal autoregulation in patients with RVH. A probable reason for our different observations was a substantially lower degree of renal artery stenosis and thus a lower cardiovascular risk in our study. In view of the chronic nature and haemodynamic significance of atherosclerotic renal artery stenosis found in the study of Coen *et al.*, we think that some secondary lesions, which developed in the vascular-interstitial region of the kidneys, might have been irreversible. Thus, in earlier stages of the disease and a lower degree of stenosis, the probability of regression of the functional and structural changes in intra-renal vessels is expected to be much higher.

In view of the increased cardiovascular risk, all patients with atherosclerotic renal artery stenosis should be treated pharmacologically. The current recommendations indicate ACE-I and ARB as the most effective drugs in RVH treatment [8]. Calcium channel blockers (CCB) and other antihypertensive drugs are recommended for use as the second line of treatment. In various studies, a beneficial effect of these drugs on regression of atherosclerotic lesions was found [21]. In our study, the patients were treated with 4 antihypertensive drugs on average and all of them received ACE-I and CCB (Table II). Mean blood pressure in the treated group was 95 mmHg and did not differ significantly from the control group. In the group of 195 patients with RVH, 54 of whom were treated conservatively for a mean period of 5.5 years, Losito *et al.* found that use of ACE-I was directly correlated with longer survival, in contrast to revascularisation, which did not contribute to survival prolongation [22].

In our study, we found an improvement of renal autoregulation in the group of kidneys with a non-stenosed artery owing to the use of the appropriate treatment regimen. Also the progression of the atherosclerotic process in stenosed arteries was probably inhibited, because of rather steady-state autoregulation efficiency of these kidneys, with

stable global kidney function. However, due to the lack of indications for radiological re-assessment of RAS after the period of controlled drug therapy, we cannot prove this thesis directly.

Control subjects were significantly different from patients with RAS especially in relation to age, smoking habit, hypertension, LDL, renal function and renal artery pathology. On the other hand, we did not find any significant correlations between these variables and change of ΔRI in contralateral kidneys. Moreover, the change of ΔRI did not correlate significantly with the duration of CMT. Likely, the change of ΔRI depends on many agents. One of the most important factors might be optimal antihypertensive treatment.

Although evaluations of DCT were performed after washout periods of 5 days (covering double the half-life of the used drugs), we might not have avoided the influence of the drugs. Nevertheless, a longer washout period, more appropriate for the haemodynamic study, can dangerously accelerate hypertension. With respect to this restriction the 5-day washout period seems to be the choice of optimal compromise.

If our findings are confirmed in large, randomised studies, conservative treatment may prove to be more favourable than the effect of angioplasty found by Coen *et al.* [6]. Patients treated pharmacologically along with potential invasive treatment dependent on strict clinical indications seem to obtain the best benefit, especially in improvement of renal function.

Undoubtedly, the relatively short washout period, rather young age and small size of the study group, as well as only moderate stenosis of the renal artery, limit the value of the results of the presented preliminary study. The small sample size, the major limit of this study, is partially caused by the time-consuming nature of the conducted tests, necessity of withdrawing antihypertensive medicines and missing data due to absenteeism of the patients at follow-up visits. Therefore, the results of this study cannot be applied to older patients or those with severe to critical renal artery stenosis.

The results of our study are promising and confirm the necessity of adequate antihypertensive treatment in patients with renovascular hypertension. However, with respect to the limitations, the results of the current study cannot be generalised. A much larger trial confirming our results is needed to change the recommendations for renovascular disease management. The results of the ASTRAL trial are partially consistent with our findings. The currently conducted randomised study (CORAL – Cardiovascular Outcomes in Renal Vascular Lesions) encompassing over 1000 patients with renal artery stenosis treated both pharmacologically and by angioplasty with stenting would confirm our observations [19].

Adequate medical therapy of renovascular hypertension preserved renal function and improved renal autoregulation efficiency in contralateral kidneys with a non-stenotic renal artery, but had no influence on renal autoregulation in stenotic kidneys.

References

1. Mancia G, Backer G, Dominiczak A, et al. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2007 Guidelines for the Management of Arterial Hypertension. J Hypertens 2007; 25: 1105-87
2. Working Group on Renovascular Hypertension. Detection, evaluation, and treatment of renovascular hypertension. Final report. Arch Intern Med 1987; 147:820-29.
3. Rabbia C, Valpreda S. Duplex scan sonography of renal artery stenosis. Int Angiol 2003; 22: 101-15.
4. Szczepańska-Sadowska E. Physiologic and patophysiologic mechanisms of renovascular hypertension development. In: Januszewicz A, Szmidt J, Więcek A (eds.). Renal related hypertension. Medycyna Praktyczna, Kraków 2003, 13-37.
5. Farmer CKT, Reidy J, Kalra PA, Cook PJ, Scoble J. Individual kidney function before and after renal angioplasty. Lancet 1998; 352: 288-9.
6. Coen G, Moscaritolo E, Catalano C, et al. Atherosclerotic renal artery stenosis: one year outcome of total and separate kidney function following stenting. BMC Nephrol 2004; 5: 15-22.
7. Cheung CM, Hegarty J, Kalra PA. Dilemmas in the management of renal artery stenosis. Br Med Bull 2005; 73-74: 35-55.
8. Hirsch AT, Haskal ZJ, Hertzer RN, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol 2006; 47: 1239-312.
9. White CJ, Olin JW. Diagnosis and management of atherosclerotic renal artery stenosis: improving patient selection and outcomes. Nat Clin Pract Cardiovasc Med 2009; 6: 176-90.
10. Bax L, Woittiez AJ, Kouwenberg HJ, et al. Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function: A Randomized Trial. Ann Intern Med 2009; 150: 840-8.
11. Radermacher J, Chavan A, Bleck J, et al. Use of Doppler Ultrasonography to Predict Outcome of Therapy for Renal-Artery Stenosis. N Engl J Med 2001; 344: 410-7.
12. Veglio F, Frascisco M, Melchio R, et al. Assessment of renal resistive index after captopril test by Doppler in essential and renovascular Hypertension. Kidney Int 1995; 48: 1611-6.

13. Veglio F, Provera E, Pinna E, et al. Renal resistive index after captopril test by echo-Doppler in essential hypertension. Am J Hypertens 1992; 5: 431-6.
14. Taniwaki H, Ishimura E, Kawagishi T, et al. Intrarenal hemodynamic changes after captopril test in patients with type 2 diabetes. Diabetes Care 2003; 26: 132-7.
15. Lubas A, Żelichowski G, Obroniecka I, Wańkowicz Z. Influence of controlled hypotensive therapy on renal autoregulation efficiency in the Doppler Captopril Test in patients with chronic glomerulonephritis. Pol Merk Lek 2008; 142: 289-93.
16. Oliva VL, Soulez G, Lesage D, et al. Detection of Renal Artery Stenosis with Doppler Sonography Before and After administration of Captopril: Value of Early Systolic Rise. AJR 1998; 170: 169-75.
17. Rene PC, Oliva VL, Bui BT, et al. Renal Artery Stenosis: Evaluation of Doppler US after Inhibition of Angiotensin-converting Enzyme with Captopril. Radiology 1995; 196: 675-79.
18. Riehl J, Schmitt H, Bongartz D, Bergmann D, Sieberth HG. Renal artery stenosis: evaluation with colour duplex ultrasonography. Nephrol Dial Transplant 1997; 12: 1608-14.
19. Nordmann AJ, Logan AG. Balloon angioplasty versus medical therapy for hypertensive patients with renal artery obstruction. Cochrane Database Syst Rev 2003; 3: CD002944.
20. The ASTRAL Investigators; Wheatley K, Phil D, Ives N, et al. Revascularization versus Medical Therapy for Renal-Artery Stenosis N Engl J Med 2009; 361: 1953-62.
21. Wang JG, Staessen JA, Li Y, et al. Carotid intima-media thickness and antihypertensive treatment: a meta-analysis of randomized controlled trials. Stroke 2006; 37: 1933-40.
22. Losito A, Errico R, Santirosi P, Lupattelli T, Scalera GB, Lupattelli L. Long-term follow-up of atherosclerotic renovascular disease. Beneficial effect of ACE inhibition. Nephrol Dial Transplant 2005; 20: 1604-9.