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Impact of renal artery stenting on cytokine levels, left ventricle mass and diastolic function

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Abstract

Background: Significant renal artery stenosis (RAS) may lead to left ventricle (LV) hypertrophy and diastolic function (DF) impairment through complex mechanisms: activation of cytokines and/or systolic and diastolic blood pressure (SBP, DBP) increase.

Aim: To assess interrelations between LV mass (LVM), DF and cytokines in patients undergoing renal artery stenting (PTA, percutaneous angioplasty of renal artery).

Methods: The study group comprised 72 subjects (44.4% men), 64.1 ± 9.9 years with RAS referred to PTA. SBP, DBP, transforming growth factor beta1 (TGF-β_1), aldosterone, B-type natriuretic peptide (BNP) levels and change in LVM and LVM index (LVMI) and DF (E_{vel}, e'_{vel}, E/A ratio, E/e' ratio, Ar_{time}-A_{time}) on echocardiography were assessed preprocedurally, and three and 12 months postprocedurally.

Results: TGF-β_1 level decreased from 13.3 ± 14.9 to 8.6 ± 8.0 ng/mL ($p = 0.027$), while BNP increased from 89.1 ± 86.3 to 131 ± 105 pmol/mL ($p < 0.001$). A significant reduction in LVMI in women (79.4 ± 16.9 vs. 95.7 ± 18.5 g/m^2, $p < 0.001$) and men (77.2 ± 16.8 vs. 100.1 ± 19.7 g/m^2, $p < 0.001$) was found at 12 months vs. baseline. Degree of LVM reduction correlated with baseline LVM ($p < 0.001$; $r = –0.612$) and e'_{vel} ($p = 0.05$; $r = 0.230$), but not with BP values. Among DF parameters, only e'_{vel} increased significantly at 12 months (5.54 ± 1.57 vs. 5.92 ± 1.65 cm/s; $p = 0.039$), while A/E and E/e' ratio, Ar_{time}-A_{time} remained similar ($p = 0.457$, $p = 0.283$ and $p = 0.258$). Factors associated with e'_{vel} increase ≥ 0.3 cm/s at 12 months were baseline LVM < 165 g ($p = 0.043$, RR = 1.39, CI 1.01–1.46), E_{vel} ($p = 0.015$, RR = 1.26, CI 1.15–1.52), e'_{vel} ($p < 0.001$, RR = 1.42, CI 1.18–1.7), DBP decrease > 10 mm Hg ($p = 0.055$, RR = 1.2, CI 1.0–1.44) and TGF-β_1 > 8 ng/mL ($p = 0.024$, RR = 1.24, CI 1.03–1.49) at 12 months.

Conclusions. Significant LVMI reduction was observed after PTA of RAS, but it was independent of BP reduction. e'_{vel} increase was independently associated with baseline LVM, E_{vel}, e'_{vel}, and 12 month decrease in DBP > 10 mm Hg.

Key words: renal artery stenosis, renal artery stenting, left ventricle mass and index, diastolic function, cytokines

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INTRODUCTION

Significant renal artery stenosis (RAS) causing renal parenchymal ischaemia leads to synthesis of vasoconstrictive, trophic and cytotoxic molecules, such as angiotensin II, aldosterone, and endothelin [1]. As a consequence of neurohormone release, uncontrolled hypertension and left ventricle (LV) hypertrophy (LVH) may develop [2, 3]. LVH caused by RAS is thought to be the highest compared to that caused by essential hypertension, or secondary to pheochromocytoma or hyperaldosteronism [4, 5]. There is data which suggests that increased level of angiotensin II prompts secretion of transforming growth factor beta1 (TGF-β_1), and the latter is responsible for LV remodelling and LVH in hypertensive patients [6]. In response to increased angiotensin II level, elevated capillary wedge pressure and LV overload, also B-type natriuretic peptide (BNP) is released from stretched cells of myocardium [7].

Another finding usually observed in patients with RAS is diastolic dysfunction, which may lead as a consequence to diastolic heart failure, with an annual mortality rate of 8%

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[8]. The impaired relaxation of the LV precedes the development of LVH in hypertensive patients. On the other hand, LVH, impaired coronary microcirculation and neurohormonal activation are common causes of progressive diastolic dysfunction [1].

In theory, renal artery angioplasty and stenting may reverse renal ischaemia and decrease levels of neurohormones and cytokines. However, there is limited data regarding the impact of percutaneous angioplasty of renal artery (PTA) on the LV mass (LVM), LVH and diastolic function (DF), as well as on cytokine profile [9–11].

Our study aimed to determine whether PTA of RAS leads to regression of LVH and improvement of DF, and whether there is an interaction with cytokine levels.

METHODS

Seventy-two hypertensive subjects, 32 men (44.4%), 40 women (55.6%), mean age 64.1 ± 9.9 (range 43–82) years, with RAS were referred to PTA, including 43 (59.7%) for progressive renal failure defined as progressive loss of kidney function over the span of time resulting in permanent kidney failure (estimated glomerular filtration rate — eGFR < 60 mL/min), two (2.7%) for pulmonary flash oedema, and 23 (31.9%) for arterial hypertension. At least one hypertension crisis was documented in 29 (40.2%) patients. RAS was recognised and confirmed on ultrasonography, angio-computed tomography or angio-magnetic resonance imaging and clinically evaluated in outpatient setting. Thus all subjects with a RAS diagnosis were admitted to the Department for the procedure.

The decision to perform PTA was reached after careful evaluation based on the clinical assessment, as well as angiographic, ultrasonographic and in some cases scintigraphic criteria confirming RAS severity, according to published guidelines for PTA of RAS [12].

All patients underwent technically successful PTA procedure (defined as a residual diameter stenosis of < 30% after stent placement). The periprocedural and postprocedural management of patients undergoing PTA for RAS was in accordance with the guidelines [13, 14].

Coronary artery disease, if present, had to be resolved at least three months before PTA of RAS. Patients with cardiovascular events during the follow-up, those who died, suffered from myocardial infarction or required coronary interventions during the first year after PTA, were not included into the study.

Atherosclerosis risk factors prevalence, prior cardiovascular history: myocardial infarction, stroke, prior revascularisation procedures, as well as coronary artery disease presence and severity were analysed in all subjects (Table 1).

Echocardiographic examination, 24-hour ambulatory arterial blood pressure monitoring (ABPM) and levels of TGF-β_1, aldosterone and BNP were assessed in all subjects prior to PTA, and then three and 12 months afterwards.

Table 1. Baseline characteristics of study participants

Age [years]	64.1 ± 9.9
Male	32 (44.4%)
BMI [kg/m^2]	27.4 ± 4.97
Hypertension	72 (100%)
Hypertension crisis	29 (40.2%)
Diabetes	12 (16.6%)
Hyperlipidaemia	71 (98.6%)
Current smoking	27 (37.5%)
Pulmonary flash oedema	4 (5.5%)
Coronary artery disease*	44 (61.1%)
CABG before PTA of RAS	12 (16.6%)
PCI before PTA of RAS	23 (31.9%)
eGFR [mL/min]	57.6 ± 24.3
eGFR < 60 mL/min	43 (59.7%)
Creatinine level [μmol/L]	126.7 ± 56
RAS [%]	68.4 ± 13.2
Bilateral PTA	18 (25.0%)

*Presence of at least one coronary artery stenosis causing lumen reduction > 50%; BMI — body mass index; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention; rest of abbreviations — see the text

Echocardiographic examination

Patients were examined in a supine position with a Toshiba Aplio SSA-770A echocardiographic machine (NasuWorks, Ottawara, Japan). All recordings were acquired with a multifrequency Doppler transducer placed at the cardiac apical window during normal respiration according to the guidelines of the American Society of Echocardiography (ASE) [13, 15].

LV systolic function was determined through LV ejection fraction by Simpson method and assessment of segmental contractile abnormalities with a two-dimensional echocardiography from a parasternal view [15].

From a parasternal view, LVM and LVM index (LVMI) were assessed according to the ASE-recommended formula: LVM = 0.8 {1.04 *[(LVIDd + IVSd + PWd)^3 – – (LVIDd)^3]} + 0.6, where PWd and IVSd are posterior wall thickness at the end diastole and septal wall thickness at the end diastole, respectively, and LVIDd — left ventricular internal dimension at the end diastole.

The LVMI was obtained by normalising the LVM over the body surface (BSA), according to the following equation: LVMI [g/m^2] = LVM/BSA.

Results of LVMI were analysed for women and men separately. LVH was recognised when LVMI exceeded 95 g/m^2 in women and 115 g/m^2 in men.

Diastolic function assessment included assessment of the mitral inflow (E wave and A wave velocities, A wave time, E/A ratio) and pulmonary vein flow (Ar time) on pulse Dop-

pler, as well as septal e' mitral annulus velocity (e'_{vel}) on tissue Doppler imaging (TDI). The E/e' ratio and the difference in Ar_{time}-A_{time} were calculated.

From the apical four-chamber view, the mitral inflow (peak early filling E-wave velocity; E_{vel}) and late diastolic filling A-wave velocity), the E/A ratio, and the isovolumetric relaxation time (IVRT) (derived by placing the cursor of CW Doppler in the LV outflow tract to simultaneously display the end of aortic ejection and the onset of mitral inflow) were assessed. Measurements included mitral A-wave duration. The measurements were done on the 100 mm/s sweep speed at end-expiration, and averaged over three consecutive cardiac cycles.

Measurements of pulmonary venous waveforms included peak systolic (S) velocity, peak anterograde diastolic (D) velocity, and the peak Ar velocity in late diastole. The duration of the Ar velocity was measured and the time difference between it and mitral A-wave duration: Ar_{time}-A_{time}.

The TDI was performed in the apical views to acquire mitral annular velocities. The sample volume was positioned at or 1 cm within the septal insertion sites of the mitral leaflets and adjusted as necessary (5–10 mm) to cover the longitudinal excursion of the mitral annulus in both systole and diastole. Spectral recordings were obtained at a sweep speed of 50 to 100 mm/s at end-expiration and those measurements reflected the average of ≥ 3 consecutive cardiac cycles. Velocity of the early diastolic myocardial motion (e'_{vel}) was measured. The E/e' ratio was calculated.

The assessment of the grade of diastolic dysfunction was performed according to ASE guidelines. In brief, normal DF was assumed when septal e'_{vel} exceeded 8 cm/s. Diastolic dysfunction was recognised when septal e'_{vel} was less than 8 cm/s. The diastolic dysfunction was distinguished into three grades [13]:

— In (Grade I), the parameters were E/A < 0.8, E/e' ≤ 8 and Ar_{time}-A_{time} < 0 ms.
— In (Grade II) the parameters were E/A 0.8–1.5, E/e' 9–12 and Ar_{time}-A_{time} > 30 ms.
— In (Grade III) the parameters were E/A > 2.0, E/e' ≥ 13 and Ar_{time}-A_{time} > 30 ms.

An Ar_{time}-A_{time} velocity duration > 30 ms was assumed a marker of an elevated LV end-diastolic pressure. The septal E/e' ratio of < 8 was assumed as associated with normal LV filling pressures, whereas a ratio > 15 was associated with increased filling pressures.

Renal function

This was evaluated by eGFR measured using the Cockroft-Gault formula:

— for men: eGFR = [140 – age) × body weight]/[serum creatinine concentration (mg/dL) × 72]
— for women: eGFR = [140 – age) × body weight]/[serum creatinine concentration (mg/dL) × 72] × 0.85

The results were expressed in mL/min.

Cytokine and hormone level assessment

Blood for serum and EDTA plasma was taken before, and three and 12 months after, the PTA procedure. Aldosterone concentration was determined by radioimmunometric method (CISbio, France). TGF-β_1 was measured by immunoenzymatic method (R&D, USA), and BNP by chemiluminescent method (Siemens, USA). The intra- and interassay coefficients of variation were as follows: aldosterone 8% and 6%, TGF-β_1 2.5% and 8%, BNP 2% and 2.1%, respectively.

Blood pressure assessment

Blood pressure was assessed with 24-hour ABPM prior to the PTA procedure, then at three and 12 months afterwards. The mean systolic and diastolic BP (SBP, DBP), as well as SBP and DBP loads, were assessed and analysed.

The blood lowering medications were noted and analysed with regard to their number and doses prior to PTA and afterwards.

The mean baseline number of the blood lowering medications was 3.2 ± 1.1 (range 1–7), including angiotensin converting enzyme inhibitors (ACEI) in 41 (56.9%), sartans in five (6.9%), beta-blockers in 56 (77.7%), calcium channel blockers in 40 (55.5%), diuretics in 51 (70.8%), alpha-blockers in 11 (15.2%) and imidazol receptor blockers in 14 (19.4%) subjects. Twelve subjects had at least two or more medical regimens from the same pharmacological group (e.g. two diuretics: indapamid and torasemid).

The study protocol was reviewed and approved by the local Ethics Committee and all patients signed informed consent.

Analysis

Categorical variables are reported as frequencies and percentages; continuous variables, as mean ± SD. Student's *t* tests or Wilcoxon's two-sample tests were used to compare continuous variables; χ^2 tests were used to compare categorical variables.

Bivariate correlation analysis was performed with Pearson's or coefficients to investigate whether change in LVM and DF parameters was correlated with hypertension improvement or cytokine level.

The factors associated with improvement in septal e'_{vel} or LVM reduction were initially sought with univariate analysis. Then, variables that were associated with e'_{vel} or LVM reduction at p-level < 0.1 were introduced to multivariate step-wise backward logistic regression analysis, preferably as categorical variables, whenever possible. The cut-off values for significant variables were established empirically. For those variables, a relative risk (RR) and 95% confidence intervals (95% CI) were calculated.

Differences at the level of $p < 0.05$ (two-tailed) were considered statistically significant.

RESULTS

In the whole study group, the mean SBP decreased by 6.5 mm Hg and mean DBP by 2.4 mm Hg; also SBP and DBP loads

Table 2. Left ventricular mass, left ventricular mass index, left ventricular systolic and diastolic function on echocardiography, cytokine levels and blood pressure parameters initially and three and 12 months after PTA of RAS

	Baseline	3 months	12 months	P (12 months vs. baseline)
Creatinine level [μmol/L]	126.7 ± 56	115.1 ± 62	117.0 ± 52	0.081
No of BP lowering regimens	3.2 ± 1.1	2.93 ± 1.3	2.9 ± 1.2	0.030
Systolic BP [mm Hg]	134.9 ± 19	130.4 ± 14	128.4 ± 13	0.002
Systolic BP load [%]	45.8 ± 29	41.3 ± 25	37.8 ± 24	0.031
Diastolic BP [mm Hg]	75.3 ± 11	74.2 ± 8.8	72.9 ± 9.1	0.034
Diastolic BP load [%]	28.7 ± 24	22.1 ± 18	22.0 ± 19	0.011
Cytokines level				
TGF-β [ng/mL]	13.3 ± 14.9	9.4 ± 9.4	8.6 ± 8.0	0.027
BNP [pg/mL]	89.1 ± 86.3	99 ± 121	131 ± 105	< 0.001
Aldosterone [pg/mL]	207.9 ± 240	198 ± 250	175 ± 134	0.393
LV systolic function				
LV ejection fraction [%]	60.0 ± 10.1	60.7 ± 10.1	59.2 ± 10.6	0.547
LVM, LVMI				
LVM [g]	178 ± 42	164.1 ± 38	147.7 ± 34.7	< 0.001
LVMI in women [g/m^2]	96.8 ± 18	89.5 ± 17.7	81.7 ± 17	< 0.001
LVMI in men [g/m^2]	101.7 ± 21	91.2 ± 22.8	81.4± 18.8	< 0.001
IVSd [mm]	12.1 ± 2.6	10.7 ± 2.1	10.4 ± 1.7	< 0.001
IVSs [mm]	17.1± 3.0	15.7 ± 2.7	14.6 ± 2.4	< 0.001
LV diastolic function				
No diastolic dysfunction	4 (5.5%)	8 (11.1%)	10 (13.8%)	0.091
Grade I	2 (2.7%)	3 (4.2%)	2 (2.7%)	
Grade II	25 (34.7%)	22 (30.5%)	21(29.2%)	
Grade III	41 (56.9%)	39 (54.1%)	39 (54.1%)	
LV diastolic function parameters				
E_{vel} [cm/s]	83.8 ± 25	82.3 ± 21.4	80.3 ± 24.8	0.281
E/A ratio	1.01 ± 0.39	1.03 0.46	0.98 ± 0.34	0.457
IVRT [ms]	115.0 ± 26	114.8 ± 26	113.2 ± 24	0.644
E'_{vel} [cm/s]	5.54 ± 1.57	5.83 ± 1.57	5.92 ± 1.65	0.039
E/e' ratio	16.6 ± 7.1	16.1 ± 8.1	15.4 ± 7.6	0.283
A velocity [cm/s]	87.6 ± 22.7	86.5 ± 23.7	83.3 ± 24.7	0.157
A time [ms]	164.6 ± 49	163.0 ± 44	169.2 ± 47	0.468
Ar time [ms]	143.8 ± 34.9	139.1 ± 31	137.7 ± 26	0.389
Ar_{time}-A_{time} [ms]	–23.3 ± 57.5	–23.5 ± 49.4	–34.9 ± 49	0.468

Abbreviations — see the text

decreased significantly (Table 2). The mean number of blood lowering medications was reduced from 3.2 ± 1.1 (range 1–7) at baseline to 2.9 ± 1.1 at 12 months after PTA (Table 2). However, ACEI and sartans were not withdrawn in patients.

The mean TGF-β_1 level decreased from 13.3 ± 14.9 to 8.6 ± 8.0 ng/mL (p = 0.027), while aldosterone level did not change significantly (208 ± 240 pg/mL prior to PTA and 175 ± 134 pg/mL at 12 months after PTA; p = 0.139). Surprisingly, mean BNP level increased significantly from 89.1 ± 86.3 to 131 ± 105 pmol/mL (p < 0.001; Table 2). Baseline BNP level was primarily correlated with baseline LV ejection fraction (p = 0.011, r = –0.297), and the same was noted at 12 months (p < 0.001, r = –0.454). BNP level decreased in 30 (41.7%), and increased in 42 (58.3%) subjects after PTA.

In patients in whom BNP concentration decreased after PTA, higher grade of RAS (73 ± 13.9 vs. 65.1 ± 11.8%, p = 0.012), more often bilateral RAS (53 vs. 21%, p = 0.005), higher baseline creatinine level (143 ± 70 vs. 115 ± 41 μmol/L, p = 0.04), lower eGFR (50.4 ± 20 vs. 63 ± 26 mL/min, p = 0.034), and lower DBP load at 12 months (16.1 ± 12 vs. 26.1 ± 22%, p = 0.028) were noted compared to patients in whom BNP

level increased. Also, greater degrees of SBP, DBP, SBP load and DBP load reductions were observed, although they did not reach statistical significance (–10.5 ± 20 vs. –3.4 ± 15 mm Hg, p = 0.093; –3.3 ± 10 vs. –31.6 ± 9 mm Hg, p = 0.446, –15.1 ± 33 vs. –1.9 ± 31, p = 0.091; –11.4 ± 22 vs. –3 ± 20 mm Hg, p = –0.099, respectively). However, the independent factors associated with BNP level reduction following PTA were: degree of RAS (p = 0.012, RR = 1.33, CI 1.07–1.65) and DBP load at 12 months (p = 0.028, RR = 0.78, CI 0.63–0.97).

LVH was recognised in 17 (42.5%) out of 40 women and nine (28.1%) out of 32 men before PTA, and in 15 (37.5%) and five (15.6%) at three months, and in seven (17.5%) and two (6.2%) at 12 months after PTA (p = 0.015 for women, and p = 0.02 for men at 12 months vs. baseline). The mean LVM reduction was –30.5 ± 33.6 g (range from –101 g to + 37 g) at 12 months vs. baseline (p < 0.001). Baseline LVM was correlated with initial BNP level (p = 0.006, r = 0.295), but not with aldosterone (p = 0.191, r = 0,164) or TGF-β_1 (p = 0.251, r = –0.123).

In women, LVMI decreased from initial 95.7 ± 18.5 to 79.4 ± 16.9 g/m^2 (p < 0.001) at 12 months after PTA, while in men from 100.1 ± 19.7 to 77.2 ± 16.8 g/m^2 (p < 0.001), respectively (Table 2). Degree of LVM reduction correlated with baseline LVM (p < 0.001, r = –0.612), IVSs (p < 0.001, r = –0.520), IVSd (p < 0.001, r = –0.453) and e'_{vel} (p = 0.052, r = 0.230; Table 3). There was no correlation between the degree of LVM reduction, cytokine levels and initial or final BP values, nor between degree of LVM reduction and the degree of change in mean SBP, DBP, or loads of SBP and DBP at 12 months (Table 3). In subjects in whom a significant LVM reduction was observed, thicker baseline IVSd, IVSs and higher baseline LVM as well as higher baseline SBP and SBP load, SBP and SBP load at 12 months, but lower baseline e'_{vel} and e'_{vel} at 12 months, were noted. Among these factors, the identified factors independently associated with LVM reduction of at least 30 g at 12 months vs. baseline were: high baseline LVM exceeding 190 g and IVSs thickness exceeding 18 mm (Table 4).

The LV systolic function remained similar at baseline, at three and at 12 months after PTA (LV ejection fraction: 60.0 ± 10.1 vs. 60.7 ± 10.1 vs. 59.2 ± 10.6; p = 0.547, respectively, Table 2).

Normal DF was observed initially in four (5.5%) out of 72 patients, and the number of patients with normal DF increased to ten (13.8%) after 12 months of follow-up (p = 0.091), while in the remaining 62 (86.2%) patients diastolic dysfunction persisted (Table 2).

In the whole study group, among DF parameters, only mean septal e'_{vel} increased significantly at 12 months (5.54 ± 1.57 vs. 5.92 ± 1.65 cm/s, p = 0.039), while mean A/E and E/e' ratio, mean Ar_{time}-A_{time} remained similar (p = 0.457, p = 0.283 and p = 0.258, Table 2). In subjects in whom e'_{vel} increase ≥ 0.3 cm/s at 12 months was observed, lower baseline LVM, septal e'_{vel}, E/A ratio, baseline and 12 month BNP level, as well as higher degree of SBP and DBP reduction after PTA. Among these factors, the independent ones associated with septal e'_{vel} increase ≥ 0.3 cm/s at 12 months after PTA were baseline LVM < 165 g (p = 0.043, RR = 1.21, CI 1.01–1.46), low baseline E_{vel} ≤ 90 cm/s (p = 0.015, RR = 1.26, CI 1.05–1.52), baseline septal e'_{vel} ≤ 5.5 cm/s (p < 0.001, RR = 1.42, CI 1.18–1.7) and decrease in

Table 3. Spearman's co-efficient correlations between degree of left ventricular mass change, E/e', septal e'_{vel} and blood pressure values

Correlations between the degree of LVM reduction at 12 months vs. baseline	Spearman R	P
Echocardiographic parameters		
Baseline LVM	–0.612	< 0.001
Baseline IVSd	–0.453	< 0.001
Baseline IVSs	–0.520	< 0.001
Baseline e'_{vel}	0.230	0.052
e'_{vel} at 12 months	0.247	0.037
E/e' ratio at 12 months	–0.229	0.065
Blood pressure values		
Baseline SBP	–0.216	0.068
Baseline DBP	–0.176	0.139
Baseline SBP load	–0.201	0.095
Baseline DBP load	–0.138	0.255
SBP at 12 months	–0.200	0.092
DBP at 12 months	–0.114	0.340
SBP load at 12 months	–0.193	0.105
DBP load at 12 months	–0.114	0.340
Change in SBP at 12 months vs. baseline	0.102	0.396
Change in DBP at 12 months vs. baseline	0.118	0.325
Change in SBP load at 12 months vs. baseline	0.096	0.425
Change in DBP load at 12 months vs. baseline	0.147	0.218
Cytokines level		
Baseline TGF-β	0.117	0.330
TGF-β at 12 months	0.199	0.120
Change in TGF-β at 12 months vs. baseline	0.066	0.582
Baseline BNP	–0.185	0.122
BNP at 12 months	–0.206	0.121
Change in BNP at 12 months vs. baseline	–0.138	0.260
Baseline aldosterone	–0.068	0.611
Aldosterone at 12 months	–0.104	0.436
Change in aldosterone at 12 months vs. baseline	–0.021	0.866

Abbreviations — see the text

Table 4. Multivariate stepwise backward logistic regression analysis. Predictors of left ventricular mass decrease by at least 30 g and septal e'_{vel} increase by at least 0.3 cm/s at 12 months after PTA of RAS, compared to initial respective values

	Relative risk	95% confidence interval	P
LVM decrease ≥ 30 g			
Baseline LVM ≥ 190 g	1.29	1.03–1.60	0.027
Baseline IVSs ≥ 18 mm	1.48	1.19–1.84	0.001
Septal e'_{vel} increase ≥ 0.3 cm/s			
Baseline LVM < 165 g	1.21	1.01–1.46	0.043
Baseline E_{vel} ≤ 90 cm/s	1.26	1.05–1.52	0.015
Baseline septal e'_{vel} ≤ 5.5 cm/s	1.42	1.18–1.70	< 0.001
Decrease in DBP > 11 mm Hg (12 months vs. baseline)	1.20	1.00–1.44	0.055
TGF-β > 8 ng/mL at 12 months	1.24	1.03–1.49	0.024
BNP > 120 pg/mL at 12 months	0.75	0.62–0.91	0.004

Abbreviations — see the text

DBP > 10 mm Hg at 12 months vs. baseline (p = 0.055, RR = 1.2, CI 1.0–1.44) and TGF-β_1 > 8 ng/mL (p = 0.024, RR = 1.24, CI 1.03–1.49) at 12 months (Table 4). High BNP level > 120 pg/mL at 12 months was a predictor of a lack of e'_{vel} increase (p = 0.004, RR = 0.75, CI 0.62–0.91) (Table 4).

DISCUSSION

In patients with diagnosed RAS, the need for renal artery revascularisation is debated, as the clinical outcome in terms of renal function and BP control are disappointing, as reported by large multicentre randomised trials [14, 16]. On the other hand, significant RAS is often encountered in patients with atherosclerotic stenoses in other arterial beds, e.g. coronary or carotid arteries [17, 18]. In such patients, especially, when there is evidence of poorly controlled hypertension or progressive renal failure, PTA of RAS is tempting. To date, the other potential benefits of PTA for RAS, such as LVH reduction or diastolic function improvement, have not been widely studied [9–11].

Although only about 35% of our patients in the present study had LVH, the important finding is that the evident LVM reduction during one year following PTA of RAS was observed. The degree of LVM reduction was independently related to the initial LVM and septal wall thickness at systole. The septal wall thickness exceeding 18 mm at systole before PTA might be a clinically relevant marker of favourable outcome in terms of LVM reduction. IVSs is also a parameter easier to measure and more reproducible than LVM assessment. In the studies by Symonides et al. [19] and Zeller et al. [20], the degree of LVM and LVMI reduction correlated positively with a higher baseline LVM, LVMI, and IVS thickness.

In our study, LVM reduction was not associated with reduced BP values, similarly to Zeller et al. [20], who neither observed a correlation between the degree of LVM or LVMI change and BP values. In these two studies, SBP and DBP reduction after PTA were rather mild (in our study by 6.5 and 2.4 mm Hg, respectively) but a significant reduction in the number of blood lowering medications in both studies was observed [20]. On the contrary, in studies in which LVM reduction correlated well with degree of BP lowering, the degree of BP reduction was much greater [19, 21]. In Symonides et al. [19], SBP and DBP were reduced by 20 mm Hg and 12 mm Hg, respectively. Yoshitomi et al. [21] observed that lowering of mean BP by 25 mm Hg was significantly correlated and LVMI reduction (r = 0.77, p < 0.01) in patients with unilateral RAS.

On the other hand, the reduction in BP values correlated significantly with TDI septal e'_{vel} in our present study. Lowering of DBP ≥ 10 mm Hg was an independent prognostic marker of DF improvement, in particular of TDI e'_{vel} increase. The other independent factors associated with e'_{vel} increase over 0.3 cm/s at 12 months vs. baseline were: low baseline LVM < 165 g, initial e'_{vel} ≤ 5.5 cm/s and E_{vel} ≤ 90 cm/s, as well as TGF-β_1 concentration > 8 ng/mL 12 months after PTA of RAS. BNP level > 120 pg/mL at 12 months was an important marker indicating lack of DF improvement following PTA.

Kawarada et al. [22] also reported significant e'_{vel} increase after PTA and observed decrease in E/e' ratio related to DF improvement. This finding contrasts with the study of Corriere et al. [9], who did not observe a significant change in E/e' ratio or recovery from diastolic dysfunction during follow-up. A possible explanation for these conflicting findings is the differences in patient characteristics. In our current study and the study of Kawarada et al. [22], more patients had concomitant coronary, carotid and/or peripheral artery disease, diabetes or underwent revascularisation procedures, compared to the Corriere et al. study [9, 22, 23]. Furthermore, normal DF was observed in only 5.5% of our subjects, but in 25% in the Corriere et al. study [9]. In our present study, there was a trend to significance with regard to patients in whom DF normalised after PTA of RAS (13.8%), while there was evident improvement in NYHA functional class in the Kawarada et al. study [22].

We did not find any correlations between LVM and cytokines, with the only exception being baseline LVM and initial BNP level ($p = 0.006$, $r = 0.295$). The later finding is in line with observations that plasma BNP might be a marker of LVH in hypertensive subjects, inducing suppression of plasma aldosterone. Almendral et al. [24] observed a significant correlation between LVM and TGF-β_1 level.

Interestingly, in our study, mean TGF-β_1 level decreased significantly after PTA, although this reduction was not correlated with the degree of LVM reduction. The TGF-β_1 level reduction is thought to reflect decrease in renal injury and improved renoprotection through the antisclerotic effects [24]. However, there is no data in literature about associations between PTA of RAS and TGF-β_1. We might try to extrapolate results of Laviades et al. [25], who showed that responders to angiotensin II blockers therapy have significantly lower TGF-β_1 concentration than nonresponders [25]. It is possible that PTA leads to angiotensin II level reduction, which leads to decrease of TGF-β_1 level.

There is no clear explanation for the increase of BNP level after PTA in the current study. As patients with recent cardiovascular events, including myocardial infarction, were not included into this study, it seems reasonable that change in BNP level should reflect the beneficial effect of PTA on LVM reduction, DF improvement and BP values. Our results are in contrast to the studies of Silva et al. [7] and Rastan et al. [11], that showed a significant reduction of plasma BNP concentration after PTA, and an even greater BP decrease in those who had higher baseline BNP level. In our present study, in patients with BNP level reduction after PTA, a higher degree of RAS, bilateral PTA, more impaired renal function and higher degree of BP reduction were observed.

CONCLUSIONS

PTA of RAS induces mild, though significant, BP reduction. Significant reductions of LVM and LVMI were observed in patients treated with PTA, but this was independent to the degree of BP and cytokine level reductions. A significant diastolic function improvement was seen only in a minority of subjects, although it was associated with DBP reduction and cytokine levels. The LVM reduction mechanisms following PTA of RAS need further investigation.

Conflict of interest: *none declared*

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Wpływ angioplastyki tętnic nerkowych na stężenie cytokin, masę i funkcję rozkurczową lewej komory

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Streszczenie

Wstęp: Istotne zwężenie tętnic nerkowych (RAS), powodując wzrost stężenia cytokin oraz wartości skurczowego i rozkurczowego ciśnienia tętniczego (SBP, DBP), może prowadzić do przerostu mięśnia lewej komory (LV) i upośledzenia funkcji rozkurczowej (DF) miokardium.

Cel: Celem badania była ocena wzajemnych zależności między masą LV (LVM), DF i stężeniem cytokin u chorych poddawanych stentowaniu tętnic nerkowych (PTA).

Metody: Do badania włączono 72 chorych (44,4% mężczyzn) w średnim wieku 64,1 ± 9,9 roku, z RAS po zabiegu PTA. U wszystkich chorych określano SBP, DBP, stężenia transformującego czynnika wzrostu beta1 (TGF-β_1), aldosteronu, peptydu natriuretycznego (BNP), zmiany LVM i wskaźnika masy lewej komory (LVMI), a także echokardiograficzne parametry DF, tj. (E_{vel}, e'_{vel}, współczynnik E/A, współczynnik E/e', Ar_{time}-A_{time}) przed, 3 i 12 miesięcy po PTA.

Wyniki: Po zabiegu zaobserwowano zmniejszenie stężenia TGF-β_1 z 13,3 ± 14.9 do 8,6 ± 8,0 ng/ml (p = 0,027), natomiast wzrost BNP z 89,1 ± 86,3 do 131 ± 105 pmol/ml (p < 0,001). W 12 miesięcy po zabiegu stwierdzono znamienny spadek LVMI zarówno u kobiet (79,4 ± 16,9 *vs*. 95,7 ± 18,5 g/m^2, p < 0,001), jak i u mężczyzn (77,2 ± 16,8 vs. 100,1 ± 19,7 g/m^2, p < 0,001) w porównaniu z wartościami sprzed PTA. Stopień redukcji LVM korelował z wyjściową LVM (p < 0,001; r = –0,612) i prędkością e'_{vel} (p = 0,05; r = 0,230), natomiast nie korelował z parametrami BP. Wśród parametrów DF zaobserwowano istotne zwiększenie prędkości e'_{vel} 12 miesięcy po PTA (5,54 ± 1,57 *vs*. 5,92 ± 1,65 cm/s; p = 0,039), natomiast współczynniki: A/E, E/e', Ar_{time}-A_{time} nie zmieniły się istotnie (p = 0,457; p = 0,283; p = 0,258). Czynnikami związanymi ze wzrostem prędkości e'_{vel} ≥ 0,3cm/s 12 miesięcy po PTA były: LVM < 165 g (p = 0,043; RR = 1,39; CI 1,01–1,46), E_{vel} (p = 0,015; RR = 1,26; CI 1,15–1,52) oraz e'_{vel} (p < 0,001; RR = 1,42; CI 1,18–1,7) przed zabiegiem, a także zmniejszenie DBP o co najmniej 10 mm Hg (p = 0,055; RR = 1,2; CI 1,0–1,44) i stężenie TGF-β_1 > 8 ng/ml (p = 0,024; RR = 1,24; CI 1,03–1,49) 12 miesięcy po PTA.

Wnioski: W rocznej obserwacji u chorych poddanych PTA w przebiegu RAS obserwuje się znamienną redukcję LVMI, która jednak jest niezależna od stopnia redukcji BP. Wzrost prędkości e'_{vel} jest niezależnie związany z początkową LVM, E_{vel}, i e'_{vel} oraz spadkiem DBP o co najmniej 10 mm Hg 12 miesięcy po PTA.

Słowa kluczowe: zwężenie tętnic nerkowych, ciśnienie skurczowe i rozkurczowe, lewa komora, funkcja rozkurczowa, wskaźnik masy lewej komory, stentowanie tętnic nerkowych, transformujący czynnik wzrostu beta1, peptyd natriuretyczny

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