Extra-renal factors influencing resistance index in stable kidney transplant recipients

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BACKGROUND: Increased resistance index (RI), measured in segmental arteries within the kidney graft, has been associated with decreased long-term allograft and patient survival in kidney transplant recipients (1). Moreover, RI correlates with age and markers of atherosclerosis and arterial stiffness, but not with kidney graft function (2-3). Taking into account the potential role of endothelial dysfunction, inflammatory status, arteriosclerotic lesions and target organ damage, we perform the cross-sectional study to evaluate extra-renal determinants of kidney graft resistance index in a large cohort of stable kidney transplant recipients.

PATIENTS AND METHODS: This study enrolled 174 kidney transplant recipients with a mean time after transplant of 8.2±1.8 years. Echocardiography, carotid ultrasound (intima media thickness – IMT) and the assessment of pulse wave velocity (PWV) were performed, as well as the Doppler examination of kidney graft. The inflammatory markers, adhesion molecules and NT-proBNP concentrations were measured. Patients were divided into quartile subgroups based on RI value (Q I: RI ≤0.68, Q II: RI 0.69-0.72, Q III: RI 0.73-0.76, Q IV: RI ≥0.77).

RESULTS: The analyzed subgroups were comparable with respect to demographics (except age) and anthropometric parameters, as well as comorbidities (Table 1). The values of age, serum phosphate, PWV, left ventricular mass (LVM), and LVM index (LVMI) increased in subsequent RI quartile subgroups. The strongest correlation was found between RI and age, LVM, LVMI, plasma parathormone concentration, and was negative with eGFR. In backward stepwise multivariate regression analysis, the RI variability was explained by age, LVMI, and serum phosphate concentration.

Table 1 — Patients characteristics

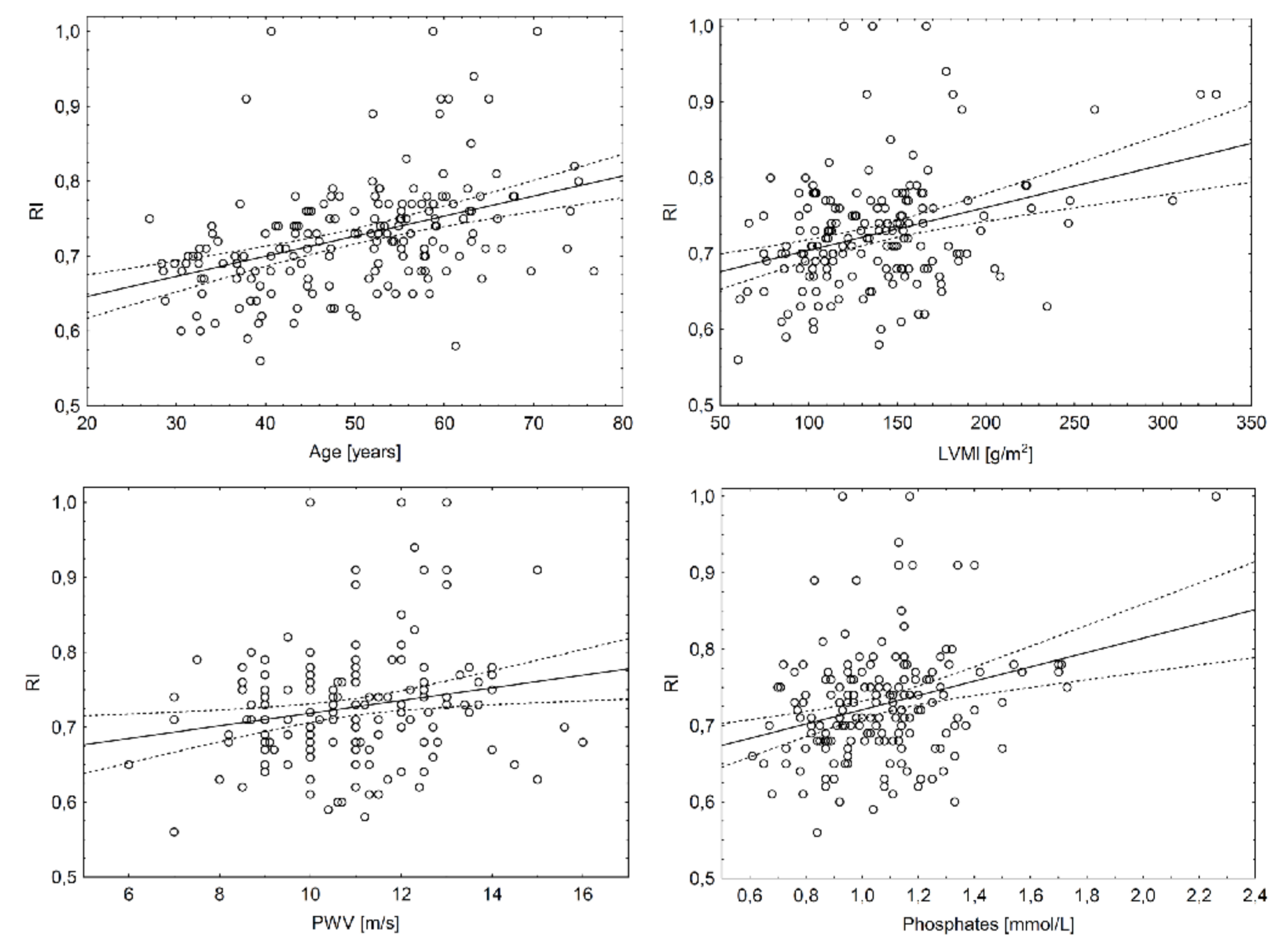|	RI ≤0.68 n=51	RI 0.69-0.72 n=41	RI 0.73-0.76 n=42	RI ≥0.77 n=40	ANOVA
Age [years]	45 (42-48)	45 (40-49)	51 (48-54)	57 (53-59)	<0.001
Gender [M/F]	35/16	23/18	28/14	21/19	NS
BMI [kg/m²]	26.4 (25.1-27.8)	25.3 (24.0-26.6)	28.0 (26.5-29.5)	27.5 (25.7-29.4)	NS
Duration of dialysis [mo]	31 (24-39)	32 (23-41)	27 (20-34)	32 (23-40)	NS
Time after transplantation [y]	8.5 (8.0-9.1)	6.8 (3.0-10.7)	8.0 (7.5-8.6)	8.4 (7.9-9.0)	NS
Hypertension [%]	94	93	98	95	NS
Diabetes n[%]	8 (15.7)	7 (17.1)	13 (31.7)	13 (32.5)	0.03
Coronary artery disease n[%]	10 (19.6)	5 (12.2)	6 (14.3)	11 (27.5)	NS
MACE n[%]	10 (19.6)	4 (9.8)	5 (11.9)	7 (17.1)	NS
Systolic BP [mmHg]	135 (131-139)	141 (135-147)	133 (128-139)	144 (139-148)	0.02
Diastolic BP [mmHg]	87 (84-89)	87 (84-90)	84 (82-86)	85 (83-88)	NS
eGFR [ml/min/1.73m²]	57.3 (51.9-62.7)	52.6 (45.3-60.0)	51.4 (44.0-58.7)	45.0 (39.1-51.0)	0.06
Calcium [mmol/L]	2,43 (2.36-2.49)	2.41 (2.37-2.45)	2.36 (2.32-2.40)	2.35 (2.28-2.42)	NS
Phosphate [mmol/L]	1.00 (0.95-1.06)	1.05 (0.99-1.10)	1.05 (0.99-1.12)	1.18 (1.08-1.28)	0.002
Parathormon [pg/ml]	140 (113-167)	153 (114-193)	170 (106-235)	251 (145-356)	0.07
Cholesterol [mmol/L]	5.6 (5.2-5.9)	5.1 (4.8-5.4)	5.7 (5.2-6.2)	5.1 (4.7-5.5)	0.04
HDL [mmol/L]	1.2 (1.1-1.4)	1.2 (1.1-1.3)	1.2 (1.1-1.3)	1.2 (1.0-1.3)	NS
Triglicerydes [mmol/L]	1.9 (1.6-2.2)	1.5 (1.3-1.7)	1.8 (1.6-2.1)	1.5 (1.3-1.8)	NS
hsCRP [mg/L]	7.0 (0.9-13.2)	3.7 (2.6-4.7)	3.9 (2.6-5.2)	5.0 (2.7-7.3)	NS
IL-6 [pg/mL]	3.7 (2.6-4.8)	4.4 (3.0-5.8)	3.7 (2.8-4.5)	4.5 (3.2-5.9)	NS
TNF-α [pg/mL]	3.0 (2.3-3.7)	2.9 (2.4-3.3)	2.5 (2.1-2.9)	3.3 (2.7-4.0)	NS
NT-proBNP [pg/mL]*	328 (118-520)	392 (214-806)	442 (213-768)	796 (288-1859)	0.02**
NT-proBNP <400 pg/mL [%]	55.3	52.5	42.1	40.0	NS

Data shown as means ± 95% CI or frequencies, *median and quartiles, ** Kruskal-Wallis test. RI: resistance index BMI: body mass index, MACE: major adverse cardiac events, BP: blood pressure, eGFR - MDRD: estimated glomerular filtration rate based on Modification of Diet in Renal Disease Study formula, HDL: high-density cholesterol, CRP: C-reactive protein, IL-6: interleukin-6, TNF-α: tumour necrosis factor alpha, NT-proBNP: N-terminal prohormone for brain natriuretic peptide.

Fig. 1

The univariate correlations between kidney graft RI and age ($r=0.365$, $p<0.001$) (A), left ventricular mass index (LVMI) ($r=0.360$, $p<0.001$) (B), pulse wave velocity (PWV) ($r=0.191$, $p<0.05$) (C), and serum phosphate ($r=0.188$, $p<0.05$) (D)

Fig. 2

The univariate correlation between pulse wave velocity (PWV) and left ventricular mass index (LVMI) ($r=0.156$, $p<0.05$)

Table 2 — The results of ultrasound and PWV examinations

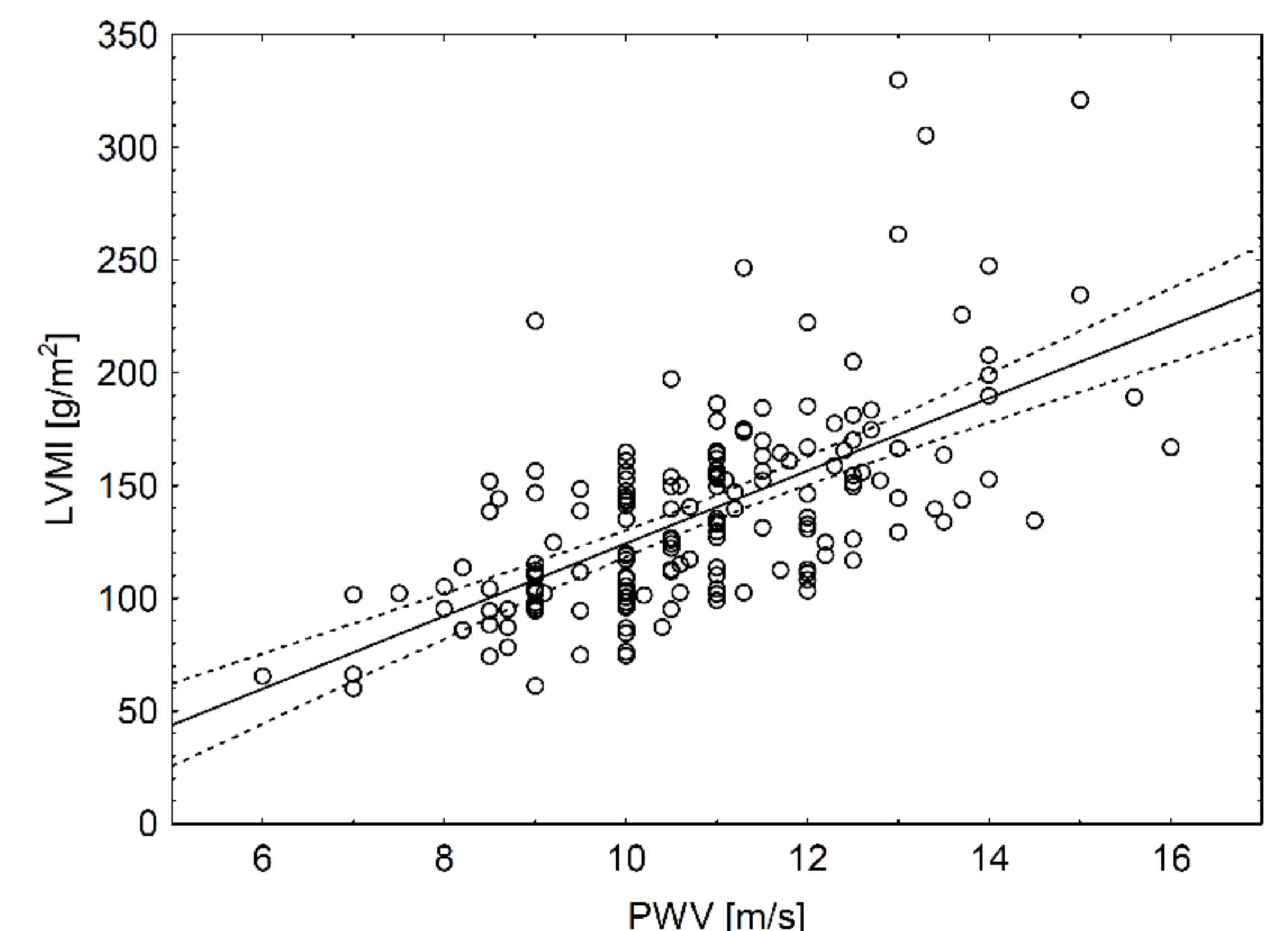|	RI ≤0.68 n=51	RI 0.69-0.72 n=41	RI 0.73-0.76 n=42	RI ≥0.77 n=40	ANOVA
IMT [mm]	0.62 (0.58-0.66)	0.62 (0.57-0.66)	0.64 (0.60-0.69)	0.66 (0.62-0.70)	NS
Calcified plaques [%]	13 (25.5%)	13 (31.7%)	17 (40.5%)	18 (45%)	0.03
PWV [m/s]	11.7 (10.6-12.7)	12.2 (10.9-13.5)	12.2 (11.0-13.5)	14.9 (12.3-17.5)	0.03
EDD [mm]	48.6 (46.9-50.3)	48.1 (46.5-49.8)	49.1 (47.3-51.0)	52.1 (50.0-54.3)	0.02
ESD [mm]	29.4 (27.8-31.0)	28.7 (27.3-30.0)	28.2 (26.5-30.0)	31.4 (29.1-33.4)	0.07
IVS [mm]	11.8 (11.3-12.4)	11.6 (10.9-12.3)	12.5 (11.6-13.4)	12.7 (11.9-13.4)	0.11
PW [mm]	10.6 (10.1-11.2)	10.6 (10.1-11.1)	10.9 (10.4-11.4)	11.2 (10.7-11.8)	0.26
LVM [g]	249 (223-275)	236 (216-256)	266 (240-292)	311 (269-352)	0.003
LVMI [g/m²]	129 (118-140)	126 (116-137)	136 (124-147)	163 (144-182)	<0.001

Data shown as means ± 95% CI or frequencies. RI: resistance index, IMT: intima-media thickness, PWV: pulse wave velocity, EDD: left ventricular end-diastolic diameter, ESD: left ventricular end-systolic diameter, IVS: intraventricular septal thickness, PW: posterior wall thickness, LVM: left ventricular mass, LVMI: left ventricular mass index.

Table 3 — The results of backward stepwise multivariate regression analysis for RI value

Independent variable	β	p
Age [per year]	0.376 (0.238-0.514)	<0.001
LVMI [per g/m²]	0.167 (0.030-0.304)	0.02
Phosphate [per mmol/l]	0.201 (0.065-0.338)	0.004
eGFR [per ml/min/1.73m²]	-0.144 (-0.282- -0.005)	0.04

CONCLUSION: Arterial stiffness and left ventricular hypertrophy may significantly influence the intrarenal vascular resistance measured using Doppler sonography in stable kidney transplant recipients. This should be taken into consideration when interpreting increased RI values in transplant patients with significant cardiovascular disease, especially when previous RI measurements are lacking.

References
1. Radermacher et al. *NEJM* 349: 115, 2003
2. Heine et al. *Kidney Int* 68: 878, 2005
3. Schwenger et al. *Am J Transplant* 5: 2721, 2005