European Journal of Preventive Cardiology

Original scientific paper

European Journal of Preventive Cardiology
2015, Vol. 22(4) 415–422
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DOI: 10.1177/2047487314524683
ejpc.sagepub.com
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Association of renal resistive index with aortic pulse wave velocity in hypertensive patients

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Abstract

Background: Recent data suggest that renal haemodynamic parameters obtained by duplex Doppler sonography, especially the intrarenal resistive index (RI), may be associated with systemic vascular changes. However, conflicting data exist about the independent relationship between aortic stiffness and RI. The aim of this study was to evaluate the relationship between RI and arterial stiffness, assessed by aortic pulse wave velocity (aPWV), in hypertensive patients.
Design: Cross-sectional study.
Methods: We enrolled 264 hypertensive subjects aged between 30 and 70 years. They were divided into two groups, either with normal renal function ($n = 140$) or with chronic kidney disease (CKD) ($n = 124$). Each patient underwent assessment of ultrasonographic renal RI and measurement of aPWV through oscillometric device.
Results: Patients with renal RI>0.7 showed higher values of aPWV, both in the overall population ($p < 0.001$) and in the subgroups with ($p < 0.01$) and without CKD ($p < 0.01$). Moreover, statistically significant correlations were observed between aPWV and RI in the whole population ($r = 0.38$, $p < 0.001$) and in the subgroups with ($r = 0.35$, $p < 0.001$) and without CKD ($r = 0.31$, $p < 0.001$). These correlations held even after adjustment for several confounding factors in multivariate analyses.
Conclusions: Our results seem to corroborate the concept that the RI may be considered as a marker of systemic vascular changes and therefore a predictor of cardiovascular risk.

Keywords

Aortic pulse wave velocity, arterial hypertension, arterial stiffness, renal Doppler ultrasonography, renal resistive index

Received 4 November 2013; accepted 27 January 2014

Introduction

The assessment of renal haemodynamic parameters by duplex Doppler sonography has been used for many years to detect changes in transplanted kidney perfusion, to diagnose renal artery stenosis, or to predict the progression of several renal diseases.[1,2] Recent data suggest that these parameters, especially the intrarenal resistive index (RI), do not only express parenchymal perfusion, but may be also associated with systemic vascular changes, hypertensive target organ damage, and an enhanced cardiovascular (CV) risk.[1–11]

In the last decade great emphasis has been placed on the role of arterial stiffness in the development of CV diseases.[12–16] Aortic pulse wave velocity (aPWV) has been proposed as the gold standard for arterial stiffness measurement, because it is easy to perform, is reproducible, and has a strong association with CV morbidity and mortality.[12–14] For these reasons, the current guidelines of the European Society of Hypertension/ European Society of Cardiology recommend aPWV

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assessment as part of individual CV risk evaluation and therapy guidance.[13]

Several studies showed that changes in aortic elastic properties are already apparent in early renal dysfunction.[12,17–19] Moreover, it has been demonstrated that aPWV increases with progressive decline of glomerular filtration rate (GFR).[12,17] However, conflicting data exist about an independent relationship between aortic stiffness and renal RI.[5–7]

The aim of this study was to evaluate the relationship between intrarenal RI and aPWV in a group of hypertensive subjects with and without chronic kidney disease (CKD).

Materials and methods

The population of this cross-sectional study was selected from 356 Caucasian hypertensive patients consecutively attending our outpatient unit of nephrology and hypertension. Written informed consent was obtained from each subject and the study was approved by the local review board.

The exclusion criteria were: (i) age <30 years or >70 years; (ii) renovascular, malignant, or endocrine hypertension ; (iii) severe obesity, defined as a body mass index (BMI) $\geq$40 kg/m^2; (iv) end-stage renal disease (stage V of Kidney Disease Outcomes Quality Initiative, KDOQI, classification);[20] (v) rapid deterioration of renal function (decrease in GFR>25% within 7 days); (vi) hydronephrosis of grade 2 or higher; (vii) significant difference in size or morphology between kidneys; (viii) permanent atrial fibrillation; (ix) heart rate >100 bpm or <50 bpm; (x) heart failure; (xi) moderate-to-severe aortic/mitral valve disease; (xii) major noncardiovascular diseases; and (xiii) low-quality renal sonographic and aPWV recordings.

Body weight and height were measured by a nurse and clinic blood pressure (BP) was recorded by a doctor. Clinic BP was considered as the mean of three consecutive measurements obtained at 2-min intervals by an electronic oscillometric validated device (Microlife Watch BP Office),[21] after 5 min of rest in sitting position. A few minutes later, aPWV measurement was performed. On the same day, a renal Doppler ultrasonographic examination and 24-h ambulatory BP monitoring (portable, noninvasive SpaceLabs 90207 recorder; Redmond, Washington, USA) were carried out.

Fasting blood samples were taken to perform routine blood chemistry and a 24-h urine sample was collected to evaluate the levels of albumin excretion. GFR was estimated by using the CKD-EPI (Chronic Kidney Disease-Epidemiology Collaboration) equation.[22]

Pulse wave velocity

All measurements were performed in a supine position after 15 min rest in a quiet, temperature-controlled room. Arterial stiffness was assessed using an operator-independent, noninvasive Arteriograph system (Tensiomed, Budapest, Hungary), which has been validated against invasive and noninvasive techniques.[23,24]

aPWV measurements are performed through an upper arm BP cuff when the pressure exceeds systolic BP by 35–40 mmHg, with a completely occluded brachial artery. In this condition, the upper arm tissues are practically incompressible, so the energy of central pressure fluctuations propagates through the conduit arteries (subclavian, axillary, brachial) and reaches the skin/overpressurized cuff edge, where it causes very small volume/pressure changes in the cuff, which are recorded by a high-fidelity pressure sensor in the device. During systole, blood volume ejected into the aorta generates a direct (or primary) systolic wave. As this pulse wave runs down the periphery, it reflects from the bifurcation of the aorta, creating a second reflected (or late) systolic wave. The return time (RT, seconds) of the pulse waves is calculated as the time difference between the first and the reflected systolic wave. aPWV (expressed in m/s) is computed from this transit time and the distance travelled by the pulse wave. Estimation of the distance travelled by the pulse wave (from the heart to the bifurcation and back) is based on measuring the distance between the jugulum (sternal notch) and the pubic symphysis (jug–Sy, metres), using a tape measure. This distance is used because it provides the nearest value of the true aortic length. aPWV is so calculated with the formula: $aPWV = (Jug/Sy)/(RT/2)$. The RT is halved because it is the sum of the forward and the backward transit time.[23,24]

Ultrasonography

The intrarenal colour duplex ultrasonography was performed through a GE Logiq P5 PRO instrument with a 4 MHz transducer, operating at 2.5 MHz for Doppler analysis. The Doppler signal was obtained from the interlobar arteries by placing the sample volume at the level of the cortico–medullary junction. Peak systolic velocity (PSV) and telediastolic velocity (TDV) were measured, and so RI was calculated by the formula: $RI = (PSV–TDV)/PSV$. The values were computed as the average of six measurements (three from each kidney). The Doppler angle chosen was less than 60°, and special care was taken not to compress the kidney and not to have the patient perform a Valsalva manoeuver, because both can increase the renal RI. A single well-trained operator (CG), unaware of the patient's clinical data, performed the ultrasound examination.

Statistical analysis

A total of 92 subjects met the exclusion criteria. Therefore, the final analysis involved 264 patients. Statistical analysis was initially performed in the whole study population. Subsequently, this was divided into two groups according to whether the study subjects had normal renal function ($n = 140$) or stage I–IV CKD ($n = 124$), so defined in line with the KDOQI criteria.[20] The overall population and each group were further subdivided in subsets on the basis of the values of renal RI ($\geq$or <0.7) and of aPWV ($>$or ≤ 10 m/s). We have chosen a cut off of 0.7 for renal RI because it has been demonstrated in previous investigations that subjects with a renal RI above this value had an increased prevalence of hypertensive target organ damage[5] and a faster progression of renal diseases.[2] aPWV >10 m/s was chosen to identify subjects with prognostic validated alterations of aortic elastic properties, as suggested by 2013 guidelines of the European Society of Hypertension.[13]

Continuous variables were given as mean $\pm$ SD. Albuminuria and triglycerides were expressed as median and interquartile range because of their skewed distribution. They were log-transformed before starting the statistical tests. Dichotomous variables were expressed as percentage values. Student's t test for independent samples was used to compare continuous variables between groups, whereas chi-squared test or Fisher's exact test, as appropriate, was used to compare categorical variables.

The univariate and multivariate relationships between renal RI, aPWV, and other variables were tested by simple and multiple linear regression analyses. The strength of the associations between the variables was expressed respectively by the Pearson correlation coefficients (r) and the standardized multiple regression coefficients (β). To compare correlation coefficients and slopes of the regression lines relating aPWV and RI in the subgroups with and without CKD, we used respectively Fisher r-to-z transformation and Student's t test for independent samples. The stepwise multiple regression models were built considering renal RI as outcome variables and including into the models as independent variables, besides aPWV, age, GFR, albuminuria, serum uric acid, smoking habit, serum glucose levels (or diabetes as dichotomous variable), triglycerides, HDLc, systolic BP (clinic or 24 h), antihypertensive drug therapy (coded as follows: 0, no treatment; 1, RAS-blocking; 2, diuretics; 3, calcium-channel blockers; 4, β-blockers or $\alpha\beta$-blockers; 5, other antiadrenergic drugs; 6, combination of two or more drugs), antiplatelet therapy (0, no treatment; 1, treatment), statin therapy (0, no treatment; 1, treatment), and, in CKD patients, also serum phosphate.

In all multiple regression analyses a backward stepwise procedure was used, with $\alpha = 0.15$ as the cut off for entry or removal of variables, which is the default value of the SYSTAT statistical package. The null hypothesis was rejected at a two-tailed $P \leq 0.05$. The statistical analyses were performed using the SYSTAT DATA version 13 (Systat, Chicago, IL, USA).

Results

Among the 124 patients with CKD, 44% had hypertensive nephropathy, 30% diabetic nephropathy, 17% unknown nephropathy, 8% chronic glomerulonephritis, and <1% cryoglobulinemia.

The main clinical characteristics of the overall study population and of the groups with and without CKD are summarized in Table 1. RI and aPWV in subjects with CKD were significantly greater than in those without CKD (both $p < 0.001$). Similarly, the percentages of patients with RI ≥ 0.7 and with aPWV >10 m/s in subgroup with CKD were higher than in that without CKD (both $p < 0.0001$).

The patients with aPWV >10 m/s, compared to those with lower aPWV, showed higher values of renal RI, both in the whole study population (0.66 ± 0.06 vs. 0.62 ± 0.07; $p < 0.001$) and in the two groups with (0.67 ± 0.06 vs. 0.63 ± 0.08; $p = 0.01$) and without CKD (0.64 ± 0.07 vs. 0.61 ± 0.06; $p = 0.01$). Similarly, higher values of aPWV were observed in patients with RI ≥ 0.7 in the overall population in comparison to those with lower RI (12.6 ± 2.2 vs. 11.1 ± 2.3 m/s; $p < 0.001$), in the two groups with normal renal function (12.1 ± 2.4 vs. 10.7 ± 2.3 m/s; $p = 0.02$), and with CKD (12.7 ± 2.2 vs. 11.8 ± 2.3 m/s; $p = 0.03$).

Table 2 shows the percentage of patients treated with CV drugs. As compared with patients without CKD, a greater proportion of CKD patients were treated with all classes of CV drugs, except for ACE-inhibitors and adrenergic receptor blockers. Table 3 shows the correlations between aPWV and intrarenal RI with other variables, both in the whole study population and in the two groups with and without CKD.

Age was the stronger correlate of aPWV and of intrarenal RI in all subjects studied, regardless of renal function. Moreover, as shown in Figure 1, the renal RI was significantly correlated with the aPWV ($r = 0.378$, $p < 0.001$) in the entire study population, in patients with CKD ($r = 0.350$, $p < 0.001$), and in those with normal renal function ($r = 0.309$, $p < 0.001$). The correlation coefficients and the slopes of the regression lines in subjects with and without CKD did not differ significantly ($p = 0.71$ and $p = 0.73$, respectively). These associations remained statistically significant in stepwise multiple linear regression analyses even after adjustment for age, estimated GFR, serum uric acid, (log) albuminuria, smoking habit, serum glucose levels,

Table 1. Demographic and clinical data of the overall study population and patients with and without CKD

	Overall population ($n = 264$)	Without CKD ($n = 140$)	With CKD ($n = 124$)	p-value
Age (years)	55 ± 16	52 ± 15	59 ± 16	<0.001
Men (%)	51.5	47.9	55.6	NS
Diabetic patients (%)	29.2	20.0	39.5	0.001
Smokers (%)	35.4	32.9	38.2	NS
Body mass index (kg/m^2)	28.0 ± 5.1	27.6 ± 5.3	28.5 ± 4.8	NS
Serum glucose (mg/dl)	101.0 ± 42.0	91.0 ± 29.4	112.5 ± 50.6	<0.001
Serum uric acid (mg/dl)	6.1 ± 2.0	5.2 ± 1.7	6.8 ± 2.1	<0.001
Total cholesterol (mg/dl)	185.7 ± 42.9	190.1 ± 34.7	181.5 ± 49.3	NS
HDL cholesterol (mg/dl)	47.4 ± 14.2	49.8 ± 12.3	45.0 ± 15.6	0.025
Triglycerides (mg/dl)	117.0 (80.0–164.3)	94.0 (73.8–131.3)	129.5 (97.0–178.5)	<0.001
LDL cholesterol (mg/dl)	111.3 ± 39.5	116.2 ± 37.4	106.6 ± 41.1	NS
Serum calcium (mg/dl)	9.2 ± 0.6	9.3 ± 0.4	9.1 ± 0.8	NS
Serum phosphorus (mg/dl)	3.7 ± 0.7	3.2 ± 0.5	4.1 ± 0.9	<0.001
Albuminuria (mg/day)	28.0 (11.9–230.0)	12.9 (4.8–21.2)	290.9 (68.0–838.5)	<0.001
Serum creatinine (mg/dl)	1.28 ± 0.96	0.86 ± 0.17	1.74 ± 1.22	<0.001
eGFR (ml/min/1.73 m^2)	73.40 ± 34.86	92.6 ± 25.9	52.2 ± 31.0	<0.001
Clinic systolic BP (mmHg)	137 ± 15	135 ± 13	141 ± 17	<0.001
Clinic diastolic BP (mmHg)	81 ± 10	82 ± 9	81 ± 11	NS
Clinic heart rate (beats/minute)	72 ± 10	73 ± 11	71 ± 9	NS
24-h systolic BP (mmHg)	129 ± 13	127 ± 12	132 ± 13	0.003
24-h diastolic BP (mmHg)	78 ± 9	78 ± 9	79 ± 8	NS
24-h mean heart rate (beats/minute)	75 ± 10	75 ± 10	74 ± 11	NS
aPWV (m/s)	11.4 ± 2.4	10.8 ± 2.3	12.1 ± 2.3	<0.001
Renal RI	0.65 ± 0.07	0.63 ± 0.07	0.67 ± 0.06	<0.001
Subjects with aPWV >10 m/s (%)	72	63	81	<0.0001
Subjects with RI ≥0.7 (%)	20.9	10.1	33.1	<0.0001

Values are mean ± SD, %, or median (interquartile range); aPWV, aortic pulse wave velocity; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, not significant; RI, resistive index.

Table 2. Cardiovascular drug treatment of the overall study population and patients with and without CKD

	Overall population ($n = 264$)	Without CKD ($n = 140$)	With CKD ($n = 124$)	p-value
Angiotensin-II receptor antagonists	23.9	17.9	30.6	0.022
ACE inhibitors	5.3	4.3	6.5	NS
Diuretics	50.8	39.3	63.7	<0.0001
Calcium antagonists	40.5	30.7	51.6	0.001
β-blockers	35.2	35.0	35.5	NS
αβ-blockers	8.3	6.4	10.5	NS
α-blockers	1.5	1.4	1.6	NS
Centrally acting antiadrenergic drugs	11.0	3.6	19.4	<0.0001
Statins	31.1	22.9	40.3	0.003
Antiplatelet drugs	22.0	15.0	29.8	0.002
Vitamin K antagonists	2.3	0.7	4.0	0.002
Allopurinol	3.1	0.0	6.5	0.007

Values are %; ACE, angiotensin-converting enzyme.

Table 3. Correlations of aPWV and intrarenal RI with other variables

	aPWV			Intrarenal RI		
Variable	Overall population	Without CKD	With CKD	Overall population	Without CKD	With CKD
Serum creatinine	0.243***	NS	0.196*	0.365***	NS	0.397***
eGFR	−0.373***	−0.215*	−0.335***	−0.406***	NS	−0.445***
Age	0.514***	0.515***	0.445***	0.450***	0.304***	0.530***
BMI	0.125*	NS	NS	0.126*	NS	NS
Serum glucose	0.246***	0.191*	0.200*	0.215***	0.231*	NS
Total cholesterol	NS	NS	−0.222*	NS	NS	NS
HDL cholesterol	−0.192**	NS	−0.210*	NS	NS	−0.208*
LDL cholesterol	NS	NS	−0.215*	NS	NS	NS
log Triglycerides	0.147*	NS	NS	0.146*	NS	NS
Serum uric acid	0.254***	NS	0.198*	0.348***	NS	0.332***
log Albuminuria	0.328***	0.341***	NS	0.307***	NS	NS
Clinic systolic BP	0.371***	0.321***	0.355***	0.189**	NS	NS
24-h systolic BP	0.294***	0.167*	0.361***	0.196**	NS	NS

NS, $p > 0.05$; *$p < 0.05$; **$p < 0.01$; ***$p \leq 0.001$; aPWV, aortic pulse wave velocity; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, not significant; RI, resistive index.

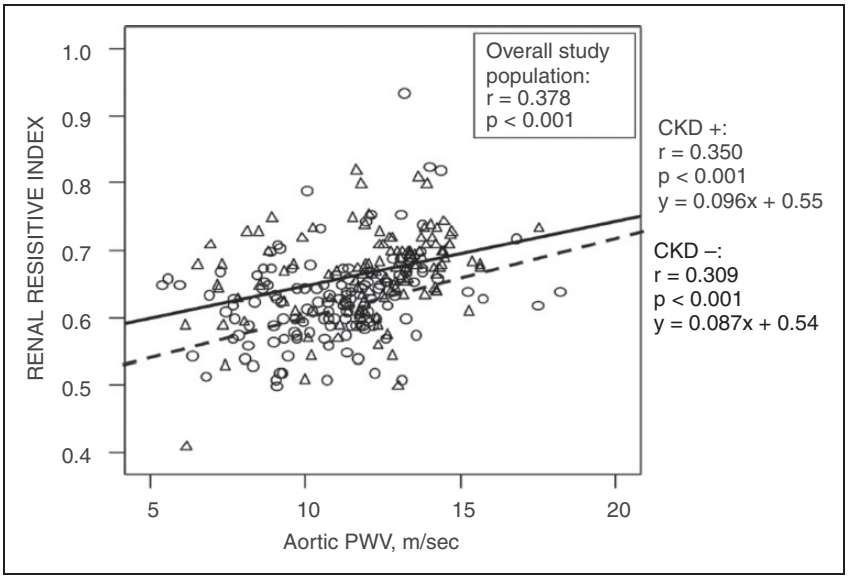

Figure 1. Relationships between aortic pulse wave velocity (PWV) and renal resistive index (RI) in overall study population and in the two groups of patients with (CKD+) and without (CKD–) chronic kidney disease (CKD). Circles indicate hypertensive patients with normal renal function; triangles indicate patients with CKD. Regression equations relating PWV and RI are also calculated: continuous line for CKD+ and broken line for CKD–.

log-triglycerides, HDLc, systolic BP (clinic or 24-h), antihypertensive drug therapy, antiplatelet therapy, statin therapy, and, in CKD patients, also serum phosphate. The standardized regression coefficients (β) relating aPWV with renal RI were 0.23 ($p < 0.01$) in the overall population, 0.19 ($p < 0.05$) in patients with CKD, and 0.25 ($p < 0.05$) in subjects without CKD.

Discussion

The main finding of our study, conducted in hypertensive patients with and without impaired renal function, is that the intrarenal resistive index, detected by Doppler ultrasound, is significantly and positively associated with large arterial stiffness, determined by

measuring the aPWV. This close association remained statistically significant even after adjustment for several potential confounding factors such as age, BP (both when measured in a clinical setting or recorded by ambulatory BP monitoring), albuminuria, GFR, metabolic parameters, therapy with antihypertensive drugs, statins and antiplatelet drugs, and also serum phosphate in CKD patients. Moreover, our results suggest that RI may be elevated in hypertensive patients, even without CKD, and progressively increases as renal function deteriorates.

Our findings seem to be in agreement with several lines of evidence suggesting that resistance index, detected at the level of the intrarenal arterial district, may be related with some markers of systemic atherosclerosis, such as the intima–media thickness, measured at the level of the common carotid artery.[2–4] However, the studies exploring the relationship between arterial stiffness and intraparenchymal renal RI yielded conflicting results.[5–7]

In 245 subjects with and without renal disease, Otha et al.[7] observed a statistically significant univariate correlation between RI and brachial–ankle PWV (a hybrid measure of both central and peripheral stiffness). Nevertheless, this association was lost after adjustment for various confounding factors in multiple regression analysis, and only the correlation between brachial–ankle PWV and extraparenchymal RI remained, with borderline statistical significance ($p = 0.044$).[7] On the contrary, in another study of 76 patients undergoing renal transplantation, intraparenchymal RI of the transplanted kidney was closely and independently related with carotid–femoral PWV of the recipient, but not with the GFR.[6] More recently, Hashimoto and Ito[8] found, in 133 hypertensive patients, significant associations between intraparenchymal RI, aPWV, and central pulse pressure (PP), even after adjustment for age, cholesterol, HbA1c, and GFR. However, it is interesting to note that no correlation was found between RI and indices of stiffness of muscular-type arterial districts, such as the carotid–radial PWV and femoro–tibial PWV,[8] which have a pathophysiological and prognostic relevance undoubtedly lower than the stiffness of a large elastic artery such as the aorta.[12]

Moreover, in 168 untreated primary hypertensive patients, Ratto et al.[25] found a relationship between RI and an ambulatory BP monitoring-derived measure of systemic vascular stiffness (Ambulatory Arterial Stiffness Index), endowed with CV prognostic significance. Furthermore, it is worth mentioning that the same research group has recently found an association between RI and an increased incidence of new-onset diabetes mellitus.[26]

All these studies, together with our findings, highlighting a close relation between impaired intrarenal haemodynamics and indices of systemic vascular damage, may contribute to explain the results of some recent investigations.[9–11] In particular, a recent study, conducted in hypertensive patients,[11] showed that the intrarenal RI is a powerful independent predictor not only of adverse renal outcomes, but also of fatal and nonfatal CV events. Similar conclusions were attained in two other studies performed in 870 elderly Americans[9] and in 90 French patients with heart failure.[10]

The cross-sectional design of our study does not allow us to establish neither causal links between renal RI and aPWV, nor the direction of this relationship. However, it seems reasonable to suggest some hypotheses to explain the association between these two variables. A possible mechanism may be that increased arterial stiffness might predispose the renal circulation to a greater haemodynamic pressure, PP more than mean arterial pressure, leading to higher renal vascular resistance.[17,27] Interestingly, previous observations suggest that the pulse wave travels with little damping from the central aorta down to the renal resistance microvessels.[27] Moreover, this interpretation is in keeping with the observation that the pulsatile (rather than steady) pressure stimulates the myogenic response of renal afferent arterioles to increase vascular resistance.[28] Another possible explanation concerning the relationship between renal RI and aPWV may be that higher renal RI may in the long term contribute to systemic arterial stiffening, possibly through renal dysfunction.[17]

Furthermore, as suggested by Hashimoto and Ito,[8] it can be assumed that the RI is itself expression of renal pulsatile flow. Analysing the formula used to calculate the RI, in fact, it is clear that it represents an index of pulsatile arterial flow and can increase both due to a relative increase in systolic flow or a relative reduction of the diastolic flow. According to this hypothesis, the aortic PP would directly result in the renal pulsatile flow. This interpretation may explain the known dependence of the RI by extrarenal factors such as age, heart rate, and the Valsalva manoeuver, which are able to influence the central PP.[1,2] It is important to note that, in renal allograft recipients, renal Doppler indices correlated significantly with the age of the recipient but not with the age of the donor,[6] suggesting that extrarenal factors such as the stiffness of the prerenal vessels (e.g. the aorta) have a major effect on renal RI. In addition, this hypothesis seems to be in accordance with the experimental evidence that PP is more important than renal vascular resistance in determining the RI in isolated perfused rabbit kidneys.[29]

In conclusion, the results of our study show a strong independent association between intrarenal RI and aPWV and seem to confirm that renal resistive index

may be considered, not only as a prognosticator of renal outcomes, but also as a marker of systemic vascular changes and therefore as a predictor of CV risk.

Funding

This work was supported by research grants in part from the University of Palermo (ex 60% ORPA07LPMC) and in part by the Italian Society of Arterial Hypertension.

Conflict of interest

The authors declare that there is no conflict of interest.

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