

Received: 2014.09.30
Accepted: 2014.12.14
Published: 2015.04.17

Renal Perfusion Index Reflects Cardiac Systolic Function in Chronic Cardio-Renal Syndrome

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Source of support: Grant No. 257 from Ministry of Science and Higher Education

Background: Cardiac dysfunction can modify renal perfusion, which is crucial to maintain sufficient kidney tissue oxygenation. Renal cortex perfusion assessed by dynamic ultrasound method is related both to renal function and cardiac hemodynamics. The aim of the study was to test the hypothesis that Renal Perfusion Index (RPI) can more closely reflect cardiac hemodynamics and differentiate etiology of chronic cardio-renal syndrome.

Material/Methods: Twenty-four patients with hypertension and chronic kidney disease (CKD) at 2–4 stage (12 with hypertensive nephropathy and 12 with CKD prior to hypertension) were enrolled in the study. Blood tests, 24-h ABPM, echocardiography, and ultrasonography with estimation of Total renal Cortical Perfusion intensity and Renal Perfusion Index (RPI) were performed.

Results: In the group of all patients, RPI correlated with left ventricular stroke volume (LVS_V), and cardiac index, but not with markers of renal function. In multiple stepwise regression analysis CKD-EPI_(Cys-Cr) (b=−0.360), LVS_V (b=0.924) and MAP (b=0.376) together independently influenced RPI (R²=0.74; p<0.0001). RPI<0.567 allowed for the identification of patients with chronic cardio-renal syndrome with sensitivity of 41.7% and specificity of 83.3%.

Conclusions: Renal perfusion index relates more strongly to cardiac output than to renal function, and could be helpful in recognizing chronic cardio-renal syndrome. Applicability of RPI in diagnosing early abnormalities in the cardio-renal axis requires further investigation.

MeSH Keywords: **Cardio-Renal Syndrome • Hypertension, Renal • Perfusion Imaging • Renal Insufficiency, Chronic**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/892630>

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Background

Despite the growing amount of literature concerning cardio-renal syndrome (CRS), certain stages of pathogenesis and the possibility of its diagnosis remain unclear [1]. Suspicion of CRS seems to be obvious in the presence of apparent kidney or heart damage with accompanying second organ dysfunction. Diagnostic difficulties arise at the stage preceding the clinical manifestation of disease, or in the case of dysfunction of only 1 of the organs, while function of the second organ does not arouse suspicion and does not require intervention. However, even minor sub-clinical pathological changes at the functional level in 1 of the organs can cause changes in the functioning of the other 1. Renal perfusion disorders are an important element in the pathogenesis of cardio-renal syndrome [1]. Properly preserved renal perfusion determines the appropriate organ tissue oxygenation [2]. Both the reduction and excessive increase in renal perfusion result in the decrease of tissues oxygenation and the onset of fibrosis. Left ventricular heart failure results in the reduction in renal perfusion and the launch of compensatory mechanisms, improving cardiac output in order to restore normal organ perfusion [3]. On the other hand, pathological processes primarily concerning kidneys significantly modify the perfusion, leading to progressive organ function impairment. Chronic kidney disease (CKD) results in the impaired salt excretion, water retention, neuro-hormonal activation, and worsening of blood pressure control. These factors are considered the main reasons for the development of chronic cardio-renal syndrome [1,4]. Therefore, the evaluation of renal perfusion parameters may be important for the early diagnosis of the disorders in the cardio-renal axis.

So far, most of the attempts of non-invasive Doppler assessment of renal perfusion were based on the measurement of renal resistive index (RI) [5]. Although the renal resistive index assessed by Doppler examination is an acknowledged marker of vascular-organ damage in cardiovascular diseases, in most cases its value does not match the organ perfusion [6]. Even though the usefulness of RI was proven in monitoring of the effectiveness of hypertension treatment, predicting a response to immunosuppressive treatment of glomerulonephritis as well as diagnosis of renal artery stenosis, the specificity of RI for the recognition of cardiovascular changes decreases with the progression of renal disease [6–9]. Another feature limiting the usefulness of RI is the measurement made in single and well-visualized segmental artery, which results in obvious omission of vessels with lower flow and often overestimates the result. If this error is irrelevant to the determination of inflow reduction as it is in the diagnosis of renal artery stenosis, it may be important for other applications of RI. In contrast, the method of Dynamic Tissue Perfusion Measurement (DTPM) reflects the size of renal perfusion and includes all of the blood flow in the tested area [5].

The aim of the study was to test a hypothesis whether Renal Perfusion Index (RPI) could relate stronger to cardiac hemodynamics than to renal function and could differentiate etiology of chronic cardio-renal syndrome.

Material and Methods

Twenty-four patients with hypertension and stable chronic kidney disease at 2-4 stage were enrolled in the study. Patients were recruited from consecutive subjects who had been admitted to the Nephrology Department over an 18-month period. Exclusion criteria included: acute renal and cardiac diseases, history of renal artery stenosis, CKD stage 5, heart failure in NYHA IV stage, atrial fibrillation, hyperkinetic state, inflammation, connective tissue diseases, vasculitis, diabetes mellitus, amyloidosis, visceral obesity, hydronephrosis, systemic cancer, lack of good quality ultrasound imaging of renal or heart structures. A total of 24 patients (4 F; 20 M; age 50 ± 17 , BMI 27.02 ± 3.44 kg/m²) performed protocol of the study. Hypertensive nephropathy (HT-CKD) referred to 12 patients. Primary diagnosis of chronic kidney disease (PCKD) was recognized in next 12 patients (9 due to glomerulonephritis, 3 of unknown etiology). None of the enrolled patients had a recognized heart failure.

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

Blood tests

Serum Creatinine (Cr) and Cystatin C (Cys) were examined to calculate glomerular filtration rate with the use of CKD-EPI formula [10]. In addition, biochemical cardiac markers such as NT-proBNP and Troponin I were collected.

Urinary albumin excretion ratio

In a random urine spot sample albumin and creatinine were tested, then albumin to creatinine ratio (mg/mg) was calculated.

Blood pressure monitoring

The 24-h Ambulatory Blood Pressure Monitoring (ABPM-04, Meditech, Hungary) was performed and the mean of 24-h systolic and diastolic blood pressure (SBP, DBP), pulse pressure (PP) and mean arterial pressure (MAP) were recorded.

Color Doppler sonography

Logiq P6 (GE) ultrasound equipment with a convex transducer 4L (2–5 MHz) was used to perform kidney ultrasound

measurements. Longitudinal sections of the right kidneys were examined and recorded. The right kidney was chosen because of better technical access to the mid-segment of renal cortex and to avoid alterations after renal biopsies.

Renal resistive index in segmental arteries was estimated as described before [8]. Mean value of RI was calculated from 2 or 3 measurements in the upper, middle and lower regions of the renal sinus.

Renal perfusion was estimated using DTPM method [11]. A renal perfusion intensity, achieved from recorded images of Color Doppler signal, from at least 3 full heart cycles in the chosen region of examination (ROE) was calculated automatically with the use of the software package PixelFlux (Chameleon-Software, Leipzig, Germany). Color Doppler frequency was set permanently on 3.4 MHz. The ROE was set in the mid-segment of renal cortex without focal abnormalities, in the area between the outer border of medullary pyramids and the kidney surface [11,12]. The ROE contained vessels running in straight toward the transducer, avoiding angle error corrections. A whole ROE perfusion intensity was calculated as Total Cortex Perfusion intensity (TCP). To calculate Renal Perfusion Index (RPI) the chosen ROE was divided into two equal segments: proximal and distal. The perfusion intensities of proximal (PCP) and distal (DCP) cortex were measured separately, then RPI was calculated as a decimal logarithm of PCP to DCP ratio. To determine arterial organ damage, left common carotid artery intima-media thickness (IMT) was measured using 11L transducer (10–13 MHz) [12]. The mean of 3 measurements of distal wall IMT in the distance of at least 10 mm before carotid sinus was calculated.

Cardiac sonography

For echocardiography the Vivid S6 (GE) with M4S-RS transducer (1.5–3.6 MHz) was used. All M-mode measurements were made according to recommendations of the American Society of Echocardiography [13]. The left atrial (LA) diameter was measured using M-mode methodology from the parasternal long-axis view. Left ventricular mass (LVM) was derived from the Devereux et al. formula, then indexed (LVMI) to body surface area [14]. The left ventricular ejection fraction (LVEF) was estimated by Simpson's biplane method. Left ventricular stroke volume (LVSV) and cardiac index (CI) were collected using 2D/continuous Doppler functions.

Statistical analysis

The Statistica 10 (StatSoft Inc.) software was used. The examined variables were analyzed with Pearson's or Spearman's correlation test as determined by meeting the condition of normal distribution. The T-test and U Mann-Whitney test were used to

analyze the difference between the groups. Receiver Operating Characteristic (ROC) analysis was performed to assess a diagnostic value of RPI in recognizing cardio-renal damage direction. Stepwise multiple linear regression analyses were used to determine factors independently modifying RPI.

Results

Patients with hypertensive nephropathy (HT-CKD) were older, had higher values of IMT, lower diastolic blood pressure and UACR in comparison to patients with CKD of other origins (Table 1). Although RPI was lower in the HT-CKD group than in PCKD, this difference was not significant. The number and classes of prescribed antihypertensive agents were similar in both groups (Table 2).

Considering the impact of cardiac and renal functions, and other factors on renal perfusion parameters, analysis of correlations was performed in both groups separately and in a group of all 24 patients. The results of performed tests are shown in Table 3.

After the examination of the model containing CKD-EPI_(Cys-Cr), LVSV, LVMI, LVEF, Troponin I, IMT, MAP and PP, in the HT-CKD group, stepwise multiple regression analysis showed that RPI was independently influenced by CKD-EPI_(Cys-Cr) ($b=-0.500$), LVSV ($b=0.790$) and MAP ($b=0.494$), ($R^2=0.84$; $p=0.002$).

The same regression analysis model was used in the PCKD group, and we found that only LVSV ($b=0.888$) significantly modified RPI value ($R^2=0.79$; $p<0.001$), (Figure 1).

When stepwise multiple regression analysis was repeated in the group of all 24 patients, CKD-EPI_(Cys-Cr) ($b=-0.360$), LVSV ($b=0.924$) and MAP ($b=0.376$) together independently modified RPI ($R^2=0.74$; $p<0.0001$). Prediction values of RPI based on this analysis are presented in Table 4.

To assess a diagnostic value of RPI in recognizing cardio-renal damage direction, Receiver Operating Characteristic (ROC) analysis was performed (Figure 2). The optimal RPI cut-off point was 0.567, and RPI<0.567 allowed for the identification of patients with chronic cardio-renal syndrome with sensitivity of 41.7% and specificity of 83.3% (area under curve 0.597 ± 0.122).

Discussion

The present work shows a significant impact of cardiac echocardiographic hemodynamic parameters on RPI. Recently, significant correlations of renal cortex perfusion parameters with cardiac biochemical and echocardiographic parameters as well

Table 1. Results of blood and urine sample tests, echocardiography, 2D/Doppler ultrasonography and ABPM.

Variable	All patients (n=24)	HT-CKD (n=12)	PCKD (n=12)	p-value (HT-CKD/PCKD)
Age (y)	50.46±16.82	57.58±15.50	43.33±15.51	0.035
BMI (kg/m ²)	27.02±3.44	28.20±2.61	25.85±3.86	0.094
Cystatin (mg/l)	1.67±0.66	1.63±0.58	1.71±0.75	0.792
Creatinine (mg/dl)	1.95±0.77	1.86±0.55	2.04±0.97	0.908
CKD-EPICys-Cr (ml/min/1.73 m ²)	47.17±21.28	47.67±21.09	46.67±22.40	0.844
UACR (mg/dl/mg/dl)	*0.17 (0.00–1.57)	*0.04 (0.00–0.25)	*0.54 (0.08–0.57)	0.010
Troponin I (ng/ml)	0.018±0.013	0.019±0.012	0.016±0.014	0.157
NT-proBNP (pg/ml)	123.14±108.38	156.57±139.51	89.71±51.56	0.326
LA (cm)	3.61±0.60	3.74±0.54	3.48±0.66	0.324
LVMI (g/m ²)	98.20±29.36	103.64±29.37	92.76±29.58	0.904
LVEF (%)	61.79±8.09	62.03±7.71	61.55±8.79	0.888
LVSV (ml)	111.20±47.54	116.22±48.41	106.19±48.25	0.992
CI (l/min/m ²)	3.86±1.57	4.05±1.59	3.66±1.59	0.488
RI	0.67±0.07	0.69±0.09	0.65±0.05	0.124
IMT (mm)	0.77±0.23	0.87±0.20	0.65±0.21	0.019
TCP (cm/s)	0.45±0.34	0.38±0.24	0.53±0.41	0.386
DCP (cm/s)	0.17±0.18	0.16±0.14	0.18±0.22	0.908
PCP (cm/s)	0.74±0.53	0.60±0.38	0.88±0.63	0.225
RPI	0.77±0.35	0.72±0.37	0.82±0.33	0.436
SBP (mmHg)	125.46±12.21	125.42±14.00	125.50±10.76	0.817
DBP (mmHg)	76.46±9.71	73.83±10.74	79.08±8.18	0.043
MAP (mmHg)	93.08±9.82	91.67±10.87	94.50±8.89	0.141
PP (mmHg)	48.58±7.51	50.67±8.92	46.50±5.37	0.179

BMI – body mass index; CI – cardiac index; CKD-EPI – based on Cystatin (Cys) and Ceratinine (Cr) Chronic Kidney Disease Epidemiology formula; HT-CKD – hypertensive nephropathy; IMT – intima-media thickness; LA – left atrium diameter; LVEF – left ventricular ejection fraction; LVMI – left ventricular mass index; LVSV - left ventricular stroke volume; MAP – mean arterial pressure; PCKD – CKD prior to hypertension; RPI – renal perfusion index; RI – renal resistive index; SBP, DBP - systolic, diastolic blood pressure; TCP, PCP, DCP – total, proximal, distal cortex perfusion intensity; PP – pulse pressure; UACR – urinary albumin excretion ratio; * median (range).

as renal function have been found [12]. Despite a strong dependence of distal renal cortex perfusion (DCP) on biochemical markers of cardiac function such as Troponin I and NT-proBNP, and nearly significant correlation with LVMI were demonstrated, renal function turned out to be the main factor modifying the value of DPI. In the present study, the leading influence of left ventricular stroke volume assessed in echocardiography on RPI was shown in both considered groups as well as in the group of all patients. With the exception of LVSV, in the

HT-CKD group RPI more strongly correlates with LVEF, in contrast to the PCKD group, where only relations to Troponin I and CI with RPI were more expressed. As long as LVEF is another parameter showing cardiac systolic function and CI is LVSV derivate, relations of these variables with RPI can be parallel to LVSV correlation. However, the relation of Troponin I to RPI in PCKD group remains unclear. Based on the acquired data, it could not be explained by differences in renal or cardiac function and markers of organ damage (LVMI, RRI, IMT).

Table 2. Comparison of blood pressure lowering agents in HT-CKD and PCKD groups.

Class of antihypertensive agent	HT-CKD (%)	PCKD (%)	p-value
ACE-I	36	50	0.622
ARB	45	20	0.342
CCB	55	40	0.597
BB	82	50	0.321
TD/LD	73	60	0.647
CN	18	20	0.972
A1B	27	30	0.944
ACE-I + ARB	82	70	0.751
Total number of antihypertensive drugs (n)	37	27	0.469

ACE-I – angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; A1B – α -1 adrenergic receptor blocker (doxazosin); BB – β -blocker; CCB – calcium channel blocker; CN – centrally acting agent (clonidine, α -methyldopa); LD – loop diuretic; TD – thiazide diuretic.

Finally, Troponin I did not appear to be an independent factor modifying RPI value.

The concept that the etiology of CKD in considered groups could be distinguished by RPI can be supported by the various types of renal injury. In essential hypertension, preserved renal autoregulation protects glomerular capillaries, but hypertensive damage is more expressed in preglomerular vessels [15]. Vascular damage is more evident than decrease in renal function. In hypertension and primary CKD, disrupted autoregulation promotes transmission of barotrauma to the glomeruli, which accelerates renal dysfunction, while preglomerular arteries could be preserved. In our study, with an agreement of described methodology, the proximal part of ROI contains arcuate arteries – the biggest preglomerular arteries in the whole ROI. Thus, the different etiology of CKD could affect RPI value. Based on of ROC analysis, we found that $RPI < 0.567$ allowed for the identification of patients with cardio-renal direction of damage with sensitivity of 41.7% and specificity of 83.3%.

At first, it seems that RPI, with its rather poor sensitivity is not a good marker for recognition of cardiorenal direction damage. Disturbances in the cardiorenal axis can result in both, significant (for the maintenance of normal renal perfusion) decrease in cardiac output, and hypervolemia effecting in excessive increase of preload and increased tension of the ventricles, resulting in increased levels of natriuretic peptides in serum. Examining data of right heart cauterization in 178 patients with heart failure exacerbation, Guglin at al., found significant correlation of creatinine with i.a. central venous pressure and renal perfusion pressure, but not with cardiac index or cardiac output, suggesting stronger dependence of renal dysfunction from congestion than cardiac output [16]. This could be one of the reasons that weaken predictive role of RPI in recognizing

etiology of CRS in our study. Nevertheless, in the aforementioned study of Guglin at al., Cr was higher in upper tertile of CI. This data are consistent with our findings, where RPI is mainly influenced by LSVV ($b=0.924$), and less and negatively by renal function ($b=-0.360$). Demonstrated by our study the positive correlation between RPI and LSVV despite CKD, rather corresponds with a compensatory increase in cardiac output induced by impaired renal perfusion, and not with an improvement in heart function as the organ [3]. Compensatory mechanisms appear to be the next reason responsible for low sensitivity of RPI. On the other hand, despite various etiologies, both studied groups were not different in relation to renal and cardiac function. Moreover, we investigated patients without heart failure. Thus, the study was performed in the early stage of cardio-renal axis disturbances. In these conditions the RPI diagnostic value is very promising.

In our study, we showed only mild, but significant, impact of renal function parameters on RPI. This influence could be even more important. The considered hypothesis seems to be confirmed by Scholbach et al., who studied 38 kidneys 1 year after transplantation and found a perfusion ratio (PCP to DCP) of 2.99, rising up to 5.56 in the following years, with the progress of nephropathy, which could reflect the reduction in the perfusion of the distal cortex [17]. On the other hand, in the further observation, the authors found decreasing perfusion ratio values, explained by the reduction of the renal proximal cortex perfusion. Nevertheless, observations by Scholbach et al. refer to transplanted kidney and cannot be transferred to native CKD. Firstly, graft denervation impairs the response of cardiovascular system to hypoxemia and changes in perfusion. Secondly, there may be a significant risk of renal perfusion modification by nephrotoxic drugs such as cyclosporine in patients after transplantation [18–20].

Table 3. Correlations of Renal Perfusion Index.

Variable	RPI		
	All patients (n=24)	HT-CKD (n=12)	PCKD (n=12)
Age (y)	0.049	-0.014	0.284
BMI (kg/m ²)	-0.161	-0.133	-0.109
Cystatin (mg/l)	0.007	0.371	-0.322
Creatinine (mg/dl)	-0.239	-0.095	-0.360
CKD-EPICys-Cr (ml/min/1.73 m ²)	-0.041	-0.343	0.175
UACR (mg/dl/mg/dl)	0.302	0.500	0.429
Troponin I (ng/ml)	0.361	0.175	0.660*
NT-proBNP (pg/ml)	0.278	0.413	0.280
LA (cm)	0.397	0.555	-0.073
LVMI (g/m ²)	0.383	0.378	0.462
LVEF (%)	0.136	0.762*	-0.398
LVSV (ml)	0.687*	0.657*	0.734*
CI (l/min/m ²)	0.576*	0.420	0.615*
RI	-0.052	0.021	0.009
IMT (mm)	0.108	0.084	0.433
SBP (mmHg)	0.058	0.361	-0.302
DBP (mmHg)	0.191	0.366	-0.025
MAP (mmHg)	0.156	0.349	-0.123
PP (mmHg)	0.173	0.453	-0.141
ACE-I	-0.111	-0.478	0.104
ARB	0.033	0.289	-0.087
CCB	0.094	0.231	0.000
BB	0.200	0.000	0.453
TD/LD	0.167	0.258	0.000
CN	0.020	0.596	-0.261
A1B	0.052	0.194	-0.114
ACE-I + ARB	-0.047	-0.117	0.038
Total number of antihypertensive drugs	0.131	0.238	0.019

ACE-I – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; A1B – α -1 adrenergic receptor blocker (doxazosin); BB – β -blocker; BMI – body mass index; CI – cardiac index; CCB – calcium channel blocker; CKD-EPI – based on Cystatin (Cys) and Creatinine (Cr) Chronic Kidney Disease Epidemiology formula; CN – centrally acting agent (clonidine, α -methyl dopa); HT-CKD – hypertensive nephropathy; IMT – intima-media thickness; LA – left atrium diameter; LD – loop diuretic; LVEF – left ventricular ejection fraction; LVMI – left ventricular mass index; LVSV – left ventricular stroke volume; MAP – mean arterial pressure; PCKD – CKD prior to hypertension; RPI – renal perfusion index; RI – renal resistive index; SBP, DBP – systolic, diastolic blood pressure; PP – pulse pressure; TD – thiazide diuretic; UACR – urinary albumin excretion ratio; * significance $p < 0.05$ for Spearman's coefficient.

Administration of individual antihypertensive agents in our study was similar in both considered groups. Most of the patients were treated with vasodilators such as ACE-I/ARB, and almost half of them with CCB. In analysis of correlations we

did not find significant influence of individual antihypertensive agents on RPI. This could be an effect of wide usage of vasodilators in our patients. Moreover, taking into account similar vasodilatory effect of these agents on proximal and distal

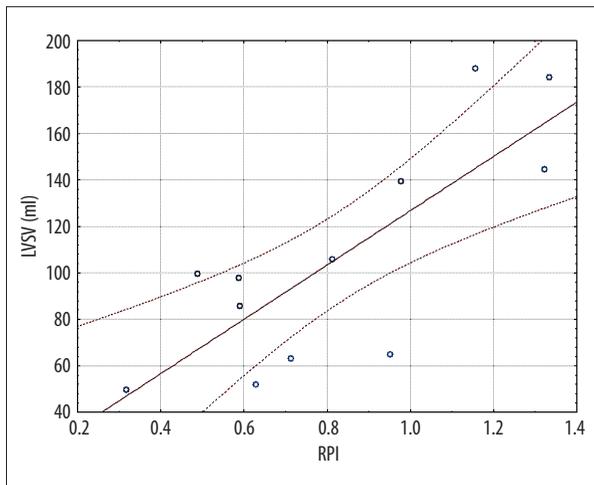


Figure 1. Linear regression of LVSF (y-axis) and RPI (x-axis) with 95% confidence interval.

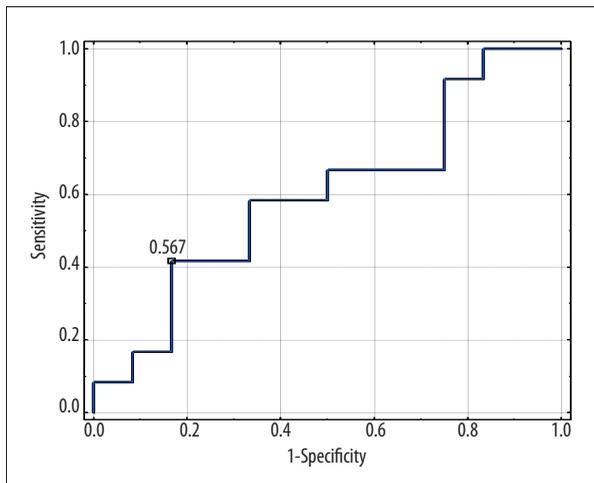


Figure 2. Receiver operating characteristic with cut-off point for RPI diagnostic value for recognizing chronic cardio-renal syndrome.

cortex arteries, calculation of RPI as PCP to DCP ratio reduces effect of these drugs on RPI. Independence of RPI from antihypertensive agents amplifies reliability of this index.

The presented data reflect the benefits from DTPM of renal cortex. We present for the first time an influence of cardiac systolic function on RPI, which is only slightly related to renal function. This finding enables probability of early, noninvasive detection of cardiac systolic abnormalities exactly at the time of kidney ultrasonography, when good quality ultrasound imaging

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Table 4. Prediction of RPI values with regard to cardiac function*.

LVSF (ml)	Predicted RPI	RPI confidence interval (-95%; +95%)
70	0.475	(0.349; 0.600)
100	0.592	(0.478; 0.705)
130	0.895	(0.799; 0.991)

* Prediction made for MAP=93 mmHg and CKD-EPI(Cys-Cr)=45 ml/min/1.73 m². LVSF – left ventricular stroke volume; RPI – renal perfusion index.

of heart structures is impossible (lack of method, emphysema, obesity). At last, it is likely that RPI evaluation could be helpful in the early recognition of cardio-renal syndrome related to lowering cardiac output and, reversely, in the prediction of renal function improvement after cardiac transplantation [21]. Nevertheless, applicability of RPI in diagnosing early abnormalities in the cardio-renal axis requires further investigation.

Although the results of our study are promising, they are still a subject to a number of serious limitations. The small size of the study group with a majority of men does not allow for a generalization of the results. In addition, the limited degree of kidney impairment in the studied group (eGFR>15 ml/min/1.73 m²) reduce the significance of our findings. Therefore, there is a need for further studies in larger groups of patients with all degrees of renal damage. Verification of our results is likely to allow for the use of ultrasound evaluation of renal perfusion in the diagnosis of cardio-renal axis disturbances.

Conclusions

Renal perfusion index relates more strongly to cardiac output than to renal function, and could be helpful in recognizing the early stage of chronic cardio-renal syndrome. Nevertheless, applicability of RPI in diagnosing abnormalities in the cardio-renal axis requires further investigation.

Conflict of interest

The authors declare that they have no conflict of interest.

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