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## Clinical Research

# The Predictive Ability of the Renal Resistive Index and Its Relationship to Duplex Ultrasound Waveform Propagation in the Aorta and Renal Arteries

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**Background:** The objective is to investigate whether calculating the PPI (Pulse Pressure Index) and the RRI (Renal Resistive Index) using routinely collected Duplex ultrasound waveforms data obtained from the aorta and renal artery correlates and predicts renal function, and determine whether RRI is affected by the presence of a renal artery stenosis.

**Methods:** The records of 965 patients were evaluated. The RRI or pulsatility index of the aorta, renal artery, hilum, cortex, and medulla were measured with concurrent glomerular filtration rate GFR, Cr, PPI, and HR measurements, among which 75 patients had a 24-hour urine measured for CrCl, and 32 patients had aortic pulse pressure index (API) calculated from the central aortic pressure measured with applanation tonometry. The propagation of the pulsatility was evaluated by Analysis of Variance (ANOVA). The correlation coefficient ( $r$ ) and the linear regression coefficient of determination  $R$ -squared ( $R^2$ ) were determined. The effects of a renal artery stenosis were evaluated with a paired  $t$ -Test comparing the RRI in 192 patients where only one side had a renal artery stenosis greater than 60%.

**Results:** The pulsatility indexes and RRIs progressively decreases and are statistically distinct by ANOVA from the aorta to the renal cortex ( $P = 7.26 \times 10^{-125}$ ). CrCl correlates with the PPI, cortex RRI and medulla RRI with  $r$  equal to  $-0.34$ ,  $-0.23$  and  $-0.42$  ( $P < 0.05$ ). GFR correlates with the PPI, cortex RRI and medulla RRI with  $r$  equal to  $-0.15$ ,  $-0.12$ , and  $-0.20$  ( $P < 0.0001$ ). Cr correlates with the PPI, cortex RRI and medulla RRI with  $r$  equal to  $0.09$ ,  $0.12$ , and  $0.14$  ( $P < 0.005$ ). The CrCl, GFR and Cr were not statistically correlated with the HR. On univariate and multivariate analysis, the  $F^2$  predictive value for PPI, cortex RRI and medulla RRI for CrCl, GFR and Cr were all less than  $0.2$  ( $P < 0.05$ ). The cortex and medulla RRI were correlated with the API with  $r = 0.63$  ( $P < 0.001$ ). The  $F^2$  predictive value of the PPI for the cortex and medulla RRI was  $0.41$  and  $0.28$  ( $P < 0.001$ ), respectively. On paired  $t$ -Test analysis renal artery stenosis had no effect on the RRI ( $P = 0.78$ ).

**Conclusions:** The RRI is calculated based on velocity waveform propagation where pulsatility slowly decreases in a series of elastic vessels. While CrCl, GFR and Cr do correlate with the

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PPI, cortex RRI and medulla RRI, the  $R^2$  coefficient of determination for these correlations demonstrate that they are poor predictors of renal function. Renal artery stenosis did not have any effect on the RRI.

## INTRODUCTION

The renal resistive index (RRI) is defined as (peak systolic velocity—end diastolic velocity)/peak systolic velocity in the cortex or medulla of the kidney<sup>1,2</sup> (Fig. 1 top), while the aortic pulsatility index (API) is defined as (peak systolic pressure—end diastolic pressure)/peak systolic pressure in the aorta<sup>3</sup> (Fig. 1 bottom). A pulse pressure index (PPI) can be similarly defined as (peak systolic pressure—end diastolic pressure)/peak systolic pressure. There have been several debates about the specific meaning and usefulness of the RRI. The RRI has been proposed as an index to determine whether the microvascular circulation within the kidney is healthy or not.<sup>4</sup> It has been thought that, low RRI indicates a healthy microvasculature within the kidney, while an elevated RRI indicates microvascular kidney disease. It has been presumed that patients with intrarenal vascular parenchymal disease would not benefit from renal artery revascularization in the presence of a renal artery stenosis.<sup>5</sup> Renal revascularization would only be expected to improve renal function and blood pressure control, if it was being done to treat renal artery stenosis in healthy kidneys otherwise. Finding a noninvasive method to determine if a kidney had intrarenal parenchymal disease might allow a study of renal revascularization in patients with a renal artery stenosis and no significant intrarenal parenchymal disease, who might benefit from renal revascularization to improve blood pressure control or renal function. Understanding the propagation, meaning, correlations, and predictive value of the flow through the aorta and renal arteries from which the RRI is measured is important to determine whether it is a useful predictor of normal renal physiology distal to any renal artery stenosis. Although it has been debated in the literature, from extensive evaluation of the RRI and renal blood flow, we hypothesized that in most clinical settings, the RRI might have limited usefulness for predicting kidneys with healthy parenchyma whose blood pressure or renal function might benefit from renal revascularization from those with unhealthy parenchyma and small artery disease that would not benefit.

A few terms require some clarification. Arteries have often been classified as elastic such as the aorta and iliac arteries or muscular such as the renal or

superficial femoral artery. None of these arteries are rigid tubes and they all have some elasticity or stretch with increased pressure. Elasticity in this paper refers to the ability of all arteries to stretch including the muscular ones. Pulse Pressure Index (PPI) is a pressure measurement, Pulsatility Index (PI) and the RRIs are flow measurements. While pressure drives flow, pressure and flow measurements have different meanings and units.

## PATIENT POPULATION AND METHODS

Institutional review board (IRB) approval was obtained to retrospectively collect anonymized data in this review of 965 patients. The IRB did not require an informed consent. Vascular laboratory data was reviewed from 2009 to 2020. RRI measurements were recalculated by two of the authors to standardize the measurements. The measurements were all done by technologists with the RVT (registered vascular technologist) credential in an IAC (Intersocietal Accreditation Commission) accredited vascular laboratory. The duplex ultrasound machine used was a Philips EPIQ 5G, with a curvilinear 3.5 MHz array transducer. The arteries were insonated at an angle less than 60°, although probe angle should not be a factor, since the pulsatility and resistive indexes are a ratio of peak systolic flow and end diastolic flow taken with the probe in an identical position. For analysis of stenosis in the aorta and renal artery, velocity measurements are taken in the adjacent aorta, renal ostium, proximal renal artery, mid renal artery, and renal hilum. The quality assurance of these measurements was confirmed by 219 patients with concurrent digital subtraction angiography, computed tomography angiography or magnetic resonance angiography with an overall accuracy of 82%. Multiple vascular lab technologists performed the renal ultrasound studies during this time period which may have led to some variability.

The PPI, renal cortex, and medulla RRI were measured for all patients with concurrent glomerular filtration rate (GFR), creatinine (Cr), pulse pressure index (PPI), and heart rate (HR) measurements in an experienced, vascular laboratory accredited by the Intersocietal Accreditation Commission where all images with concurrent radiologic studies are

### Type of Research

- Single center, retrospective analysis, observational study.

### Key Findings

- The flow velocity waveform from which the pulsatility indexes and renal resistance indexes are calculated propagate as a waveform in an elastic series of vessels. While the RRI correlates with the pulse pressure index, creatinine clearance, glomerular filtration rate and creatinine it has little predictive power for renal function in a linear regression model. It is unaffected by renal artery stenosis and does not correlate with heart rate.

### Take Home Message

- The RRI is calculated based on velocity waveform propagation and its value is related to other pulsatility indexes which slowly decrease in a series of elastic vessels. It has some correlation with creatinine clearance, glomerular filtration rate, creatinine and pulse pressure index but has limited predictive value for renal function.

### Table of Contents Summary

- The flow velocity waveform from which the renal resistive index (RRI) is calculated was found to propagate as a waveform in an elastic series of vessels. The RRI correlates with creatinine clearance, glomerular filtration rate, creatinine, pulse pressure index and the aortic pulsatility index (API) but has limited predictive value for renal function. It is independent of renal artery stenosis and not correlated with the heart rate in this retrospective, observational study. The authors suggest that a better index is needed to assess whether a kidney has normal physiologic function.

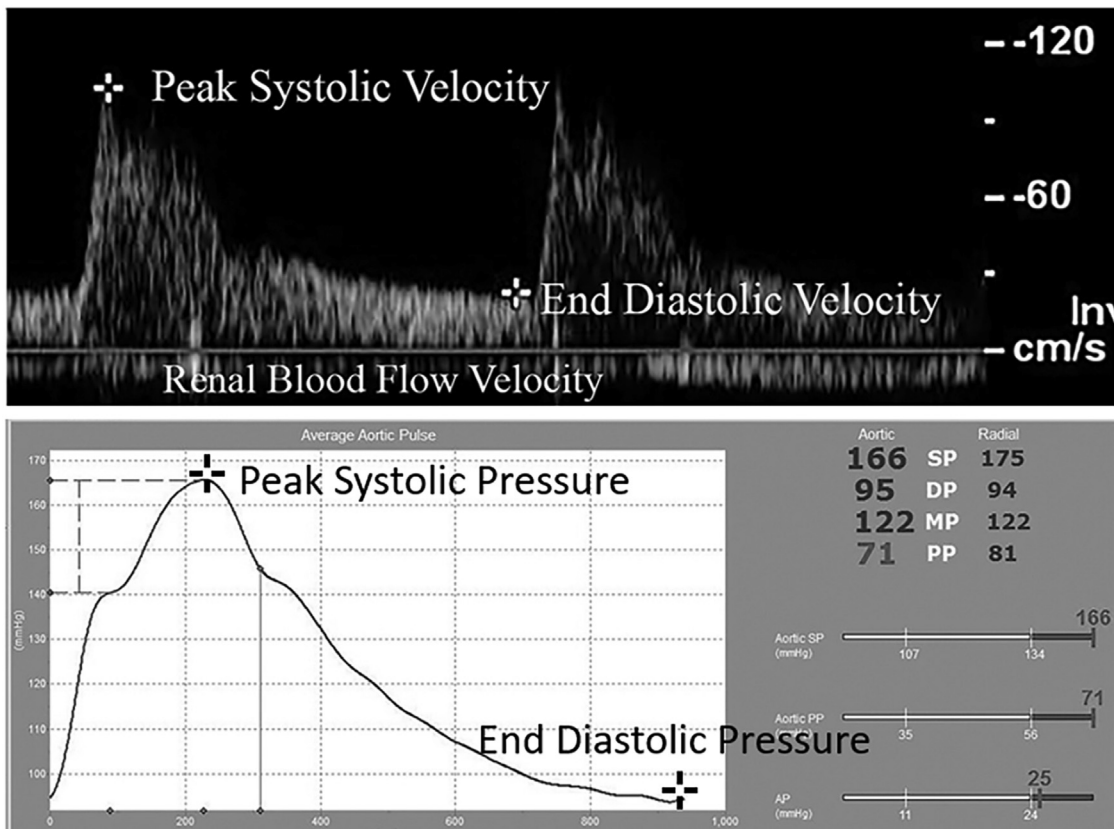
compared. The procedure is standardized for all patients. The renal medulla measurements were taken from a mid-interlobular artery and the renal cortex measurements were taken from a mid-arcuate artery. The flow pulsatility indexes or RRIs were

calculated in an identical manner for the aorta, proximal renal artery, mid-renal artery, distal renal artery, renal hilum, renal medulla, and renal cortex for the 620 of these kidneys for which all these measurements were available. Seventy-five of these patients had a concurrent 24-hour urine measurement of creatinine clearance (CrCl) and 32 patients had their API calculated from measured central aortic pressure with applanation tonometry during an experiment to quantify the renal blood flow. The API measurements were done consecutively on a subset of patients. The limited number of patients with 24-hour creatinine clearances and API measurements limits the robustness of the conclusions based on these parameters, but are similar to the findings for the glomerular filtration rate and creatinine which have much larger series of patients. [Table I](#) shows the statistical summary of the study cohort from the electronic medical record.

Applanation tonometry to measure central aortic pressure was done using the Food and Drug Administration FDA approved AtCor system. The radial artery is compressed to flatten the artery while, a strain gauge is applied on it. A mathematical formula derived from the radial pulse pressure wave and the peripheral blood pressure using a fast Fourier transformation is used to calculate the central aortic pressure. This formula has been approved by the FDA and this measurement is a standard test with reimbursement from the Centers for Medicare and Medicaid Services.<sup>6</sup> These measurements have been shown to be accurate and reproducible.<sup>7</sup> We have verified our laboratory's accuracy using catheter measured pressures.

The PIs or RRI were compared for all arterial locations using ANOVA with repeated measures.<sup>8</sup> The CrCl, GFR, Cr and HR were statistically correlated with these RRIs and the PPI measuring Pearson's correlation coefficient,  $r$ . The predictive value of the renal cortex and medulla RRI, the PPI and the HR for determining CrCl, GFR and Cr were determined by calculating the univariate and multivariate linear regression coefficient of determination R-squared ( $R^2$ ). The cortex and medulla RRIs were correlated with the PPI and the API. The predictive value of the PPI and the API on the RRI were determined with linear regression. To evaluate the effects of a renal artery stenosis, we did a paired  $t$ -Test comparing the RRI in patients where only one side had a renal artery stenosis greater than 60% evaluating 192 patients in this study.

The need for a 24-hour urine collection to determine CrCl was determined by the patient's nephrologist. The patients in this study had a clinically requested renal artery duplex ultrasound examination for hypertension or diminished renal function.



**Fig. 1.** (Top) Ultrasound image of cortical renal blood flow showing the Peak Systolic Velocity and the End Diastolic Velocity used to calculate the Renal Resistive Index

(RRI). (Bottom) Noninvasive applanation tonometry measurement of the central aortic pressure used to calculate the Aortic Pulsatility Index (API).

The applanation tonometry was done during an experiment to quantify renal blood flow. The 60% stenosis cutoff was used because there are standard duplex ultrasound criteria for determining this degree of stenosis.<sup>9</sup>

A determination of a greater than 60% renal artery stenosis was made by measuring a renal artery peak systolic velocity greater than 185 cm/sec and a renal to aortic peak systolic velocity ratio greater than 3.5.<sup>10</sup> When available, these findings were confirmed by computed tomography angiography or conventional angiography.

## RESULTS

The mean pulsatility index or RRI of the aorta, proximal renal artery, mid-renal artery, distal renal artery, renal hilum, renal medulla, and renal cortex in this cohort of patients were  $0.85 \pm 0.01$ ,  $0.80 \pm 0.01$ ,  $0.79 \pm 0.01$ ,  $0.78 \pm 0.01$ ,  $0.77 \pm 0.01$ ,  $0.74 \pm 0.01$ , and  $0.71 \pm 0.01$ . These values were statistically distinct by ANOVA with

repeated measures ( $P = 7.26 \times 10^{-125}$ ). This progressive decrease in pulsatility is identical to the dampening effect for pulsatile flow in any series of elastic vessels.<sup>11</sup> (Fig. 2)

The CrCl was correlated with the PPI, cortex RRI and medulla RRI with  $r$  equal to  $-0.34$ ,  $-0.23$  and  $-0.42$  ( $P < 0.05$ ). The GFR was correlated with the PPI, cortex RRI and medulla RRI with  $r$  equal to  $-0.15$ ,  $-0.12$ , and  $-0.20$  ( $P < 0.0001$ ). The creatinine was correlated with the PPI, cortex RRI and medulla RRI with  $r$  equal to  $0.09$ ,  $0.12$ , and  $0.14$  ( $P < 0.005$ ). A complete table of these correlations is shown in Table II. The renal cortex and medulla RRI were correlated with the API with  $r = 0.63$  ( $P < 0.01$ ). The CrCl, GFR and Cr were not statistically correlated with the HR.

On univariate linear regression, the  $R^2$  predictive value for PPI, cortex RRI and medulla RRI for the CrCl, GFR and Cr were all less than 0.2 ( $P < 0.05$ ) indicating that these variables explained less than 20% of the variation for renal function. Predictive value was not improved with multivariate linear regression. The  $R^2$  predictive value of the API for

**Table I.** Statistical summary of the study cohort

Demographics	Mean (std)/Count
Age	67.15 (12.38)
Gender	
Male	340 (35%)
Female	620 (65%)
Unknown	5 (1%)
Race	
White	830 (86%)
Black or African American	105 (11%)
Asian	22 (2%)
American Indian or Alaska Native	4 (<1%)
Unknown	4 (<1%)
Ethnicity	
Not Hispanic or Latino	927 (96%)
Hispanic or Latino	23 (2%)
Unknown	15 (2%)
BMI	28.93 (9.05)
Creatinine	1.61 (1.06)
GFR	52 (26)
Diabetes	140 (15%)
Chronic Kidney Disease	245 (25%)
Stenosis	124 (13%)

the renal cortex RRI was 0.41 ( $P < 0.001$ ) and for the medulla RRI was 0.28 ( $P < 0.001$ ). A complete table of these predictive values is shown in [Table II](#). A scatterplot of the renal cortex RRI versus the API together with its linear regression line is shown in [Figure 3](#), left. A scatterplot of the CrCl versus the renal cortex RRI together with its linear regression line is shown in [Figure 3](#), right. Scatterplots for the CrCl versus the renal medulla RRI and the CrCl versus the PPI are like the scatterplot in [Figure 3](#), right.

On paired *t*-Test analysis, a renal artery stenosis had no effect on the RRI ( $P = 0.78$ ). The mean RRI in patients with a unilateral  $>60\%$  renal artery stenosis was  $0.69 \pm 0.01$ , equal on the sides with and without a stenosis. If a renal artery stenosis would have effected the RRI, RRI would have limited value for determining, when renal function might be improved by treating a renal artery stenosis.

## DISCUSSION

Measuring the RRI has been proposed as a means of determining whether a kidney has a physiologically healthy microcirculation or not.<sup>4,5</sup> A low RRI has been presumed to be associated with a kidney with a healthy microcirculation, while an elevated RRI has been thought to indicate a physiologically unhealthy kidney. If the microcirculation within

the kidney is bad, it has been thought that revascularizing an associated renal artery stenosis would not be very beneficial. It is important to quantify the correlations and predictive values for the PPI, cortex RRI, medulla RRI and HR on renal function as measured by CrCl, GFR and Cr to determine if they are clinically useful. It is also important to determine any effects that a renal artery stenosis may have on these parameters since the stenosis itself could theoretically change their values.

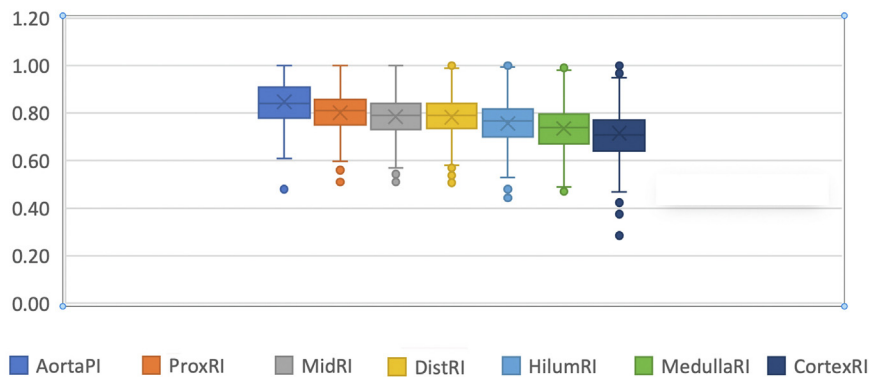
While the *P* value determines whether the correlation coefficient, *r*, or the linear regression coefficient of determination  $R^2$  is statistically significant, the values for *r* and  $R^2$  determine the strength of that relationship. As defined by the British Medical Journal<sup>12</sup> a very weak strength of correlation is defined as  $0 < r < 0.19$ , a weak correlation is defined as  $0.2 < r < 0.39$ , a moderate correlation is defined as  $0.4 < r < 0.59$ , a strong correlation is defined as  $0.6 < r < 0.79$  and a very strong correlation is defined as  $0.8 < r$ . Using this classification, the correlation between the CrCl and the medulla RRI and the medulla RRI and the PPI were within the range for a moderate correlation. The correlation for the renal cortex and medulla RRI with the API was strong. Other correlations were either weak or very weak.

The amount of variability explained by a parameter such as the PPI, renal cortex RRI or renal medulla RRI on the CrCl, GFR or Cr and the predictive usefulness for these values in a linear regression model is defined by  $R^2$ . The  $R^2$  times 100% is the percentage of the variability explained by the parameter. This study indicated that the PPI, renal cortex RRI and renal medulla RRI explained less than 20% of the values for CrCl, GFR or Cr. If over 80% of the variability of renal function is explained by factors not related to the PPI, renal cortex RRI or renal medulla RRI, then these measurements are not very useful for predicting improvement in renal function if a renal artery stenosis were treated.

Before this study, there were multiple studies evaluating smaller numbers of patients with conflicting findings. Some studies found either a weak or no correlation between the RRI and creatinine,<sup>13</sup> renal parenchymal disease,<sup>14</sup> or renal vascular resistance.<sup>15</sup> Other studies found a stronger correlation between renal function as measured by the creatinine or estimated glomerular filtration rate (eGFR) and the RRI,<sup>16–18</sup> and an association between histopathologic findings in the kidney and the RRI.<sup>19</sup>

A 24-hour urine collection for CrCl is the best common clinical measurement of renal function. While eGFR has some benefits versus creatinine

## Resistance Indexes in the Kidney



**Fig. 2.** Boxplot showing the propagation of the Pulsatility Index or Renal Resistive Index from the aorta to the renal cortex. (RI = Resistive Index).

**Table II.** A table showing the correlations and predictive values of the pulse pressure index, renal cortex RRI and renal medulla RRI for the creatinine clearance, glomerular filtration rate and the creatinine using a univariate linear regression model. The correlations and predictive values of the pulse pressure for the renal cortex RRI and renal medulla RRI are also shown.

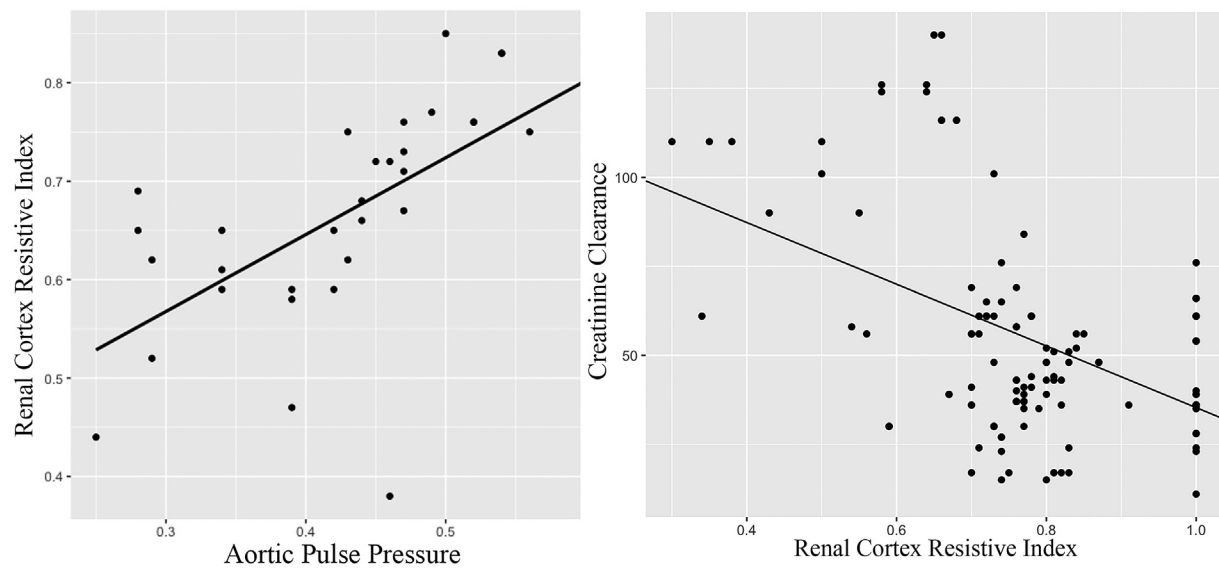
Renal parameter	Pulse pressure	Renal	
	Index	Cortex RRI	Renal medulla RRI
Creatinine Clearance	$r = 0.34$ $R^2 = 0.11$ $P = 0.009$	$r = -0.23$ $R^2 = 0.04$ $P < 0.05$	$r = -0.42$ $R^2 = 0.17$ $P < 0.0001$
Glomerular Filtration Rate	$r = -0.15$ $R^2 = 0.02$ $P < 0.0001$	$r = -0.12$ $R^2 = 0.02$ $P < 0.0001$	$r = -0.21$ $R^2 = 0.04$ $P < 0.0001$
Creatinine	$r = 0.009$ $R^2 = 0.01$ $P = 0.0013$	$r = 0.012$ $R^2 = 0.01$ $P = 0.0001$	$r = 0.14$ $R^2 = 0.02$ $P < 0.0001$
Renal Cortex RRI	$r = 0.32$ $R^2 = 0.10$ $P < 0.001$		
Renal Medulla RRI	$r = 0.40$ $R^2 = 0.15$ $P < 0.0001$		

RRI, Renal Resistance Index.

for assessing the renal function, it has been found to only have an accuracy of 57.9% in males and 33.3% in females for the assessment of normal renal function.<sup>20</sup> A search of PubMed found few other studies with limited numbers of patients evaluating the relationship between the RRI and more accurately assessing kidney function using the CrCl. One study, which included 28 patients with an abnormal creatinine clearance, demonstrated a positive relationship between the RRI and the creatinine

clearance in a multivariate regression including age and diastolic blood pressure.<sup>21</sup>

The RRI can potentially be affected by the blood pressure and flow into the kidney, any associated renal artery stenosis, and the resistance and compliance of the kidney microcirculation. Our study found that the RRI propagates in the same manner as any pulsatile flow wave in elastic tubes or vessels.<sup>11</sup> There was a strong correlation between the API as measured by applanation tomography and



**Fig. 3.** Scatterplot of the Renal Cortex Resistive Index versus aortic Pulse Pressure (*left*) and scatterplot of the Creatinine Clearance versus the Renal Cortex Resistive Index (*right*) with their regression lines.

the RRI. Previous studies have also found a relationship between the arterial or aortic pulse pressure and the RRI.<sup>22,23</sup> If the aortic waveform supplying the kidney is more pulsatile and if the RRI propagates in the same manner as other flow waveforms in an elastic tube or vessel, it would be expected that the RRI would be more pulsatile with a higher input pulsatility.

An increased pulse pressure alone has been associated with renal dysfunction.<sup>22</sup> Some of the correlation between the RRI and creatinine may be because patients with higher pulse pressures have renal dysfunction and higher RRIs because the RRI is correlated with the aortic pulse pressure. Pulse pressure is known to increase with age.<sup>24</sup> With aging, the arteries stiffen and there is a bigger difference between systolic and diastolic pressures. Renal function also declines with age.<sup>25</sup> Some of the relationship between the RRI and creatinine may be because they are both related to factors affected by aging.

Some authors have suggested that the RRI might be useful for detecting a renal arterial stenosis.<sup>26</sup> If the RRI is affected by a renal artery stenosis, its usefulness would be limited in that both the renal microcirculation and any renal artery stenosis which is present would affect it, making it difficult to differentiate whether renal dysfunction was due to a renal artery stenosis or an abnormal renal microcirculation. Our study found no significant difference in the RRI of paired kidneys where only one of the kidneys had a significant renal artery stenosis greater than 60%.

This would suggest that the RRI is not generally affected by a renal artery stenosis.

One study evaluating eight patients with a paced heart rhythm found a decrease in the RRI with increasing HR when patients were paced with increasing heart rates from 70 to 120 beats per minute.<sup>27</sup> In their study, varying HR did not affect the blood pressure or cardiac output. The authors stated that further investigation was required. It is interesting that the paced HR did not affect the blood pressure or cardiac output of these patients while another experimental study showed that these measurements were all interrelated.<sup>28</sup> Our study did not find a statistically significant correlation between the RRI and HR.

It is important to understand how the kidney microcirculation might affect the RRI. The renal microcirculation has components of both resistance and compliance.<sup>29</sup> If renal arterioles were only resistance vessels, the flow waveforms measured with the RRI would have an identical pattern to the input waveforms. The arterioles in the kidney have elasticity or compliance and resistance. The compliance allows the arterioles to expand during systole decreasing systolic flow and relax during diastole increasing diastolic flow. It is this elasticity or compliance which allows a potential change between the pulse shape in the renal artery and the pulse shape in the renal cortex or medulla. The compliance in the artery or arterioles allows blood to be stored in systole by an expansion of the vessels and released during

diastole by contraction of the vessels. The expansion and contraction of these vessels can shift the amount and timing of the flow in different arteries within the body.

To have a better physiologic assessment of the health of the kidney, it would be ideal to develop an index that separately determines the renal arterial compliance and resistance and to remove the effects of the API and pulse pressure. We are working on developing this index in our clinical studies and hemodynamics lab.

While this is the largest published study to date evaluating the PPI, renal cortex RRI, renal medulla RRI, GFR and Cr, it is a single-center study and even larger studies may be possible in the future. Larger comparisons with the CrCl would be beneficial. It has been suggested that it would be beneficial to correlate the RRI with the patient's medications and dosage. Although this would be interesting, it would be a complex undertaking since the medication effects could depend on the type of medication, dosage, and interactions between medications and how well the blood pressure was controlled with the medications, making it difficult to interpret the study results.

## CONCLUSIONS

The PI or RRI from the aorta to the renal cortex decreases in an identical manner to the flow through any elastic vessels. Although the pulse pressure, the aortic PI and the RRI correlate with renal function as measured by GFR, creatinine and creatinine clearance, the predictive value of these indexes are low and limit their usefulness in most clinical situations.

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