



## Does the measurement of the difference of resistive indexes in spleen and kidney might be used for characterization of intrarenal tardus parvus phenomenon in chronic kidney disease?



Nordeval Cavalcante Araújo\*

Ultrasound Section, Policlínica Antônio Ribeiro Netto, Rio de Janeiro, Brazil

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### ABSTRACT

Doppler sonography is used as a routine test for detection of renal artery stenosis (RAS). Although increased peak systolic velocity at the site of the narrowing is a widely accepted method for assessing main renal artery stenosis, tardus parvus phenomenon detected on the downstream blood flow has been used as an alternative to direct insonation of the main artery. However, the uncertainty about the best Doppler parameter to be used for characterization of tardus parvus has yielded a variety of studies. Recently, the difference between the resistive index of the spleen and kidney (RISK) has been proposed as a potential marker of kidney damage and Doppler criterion for RAS in hypertensive patients without chronic kidney disease (CKD). The hypothesis of this study was to speculate further and propose the RISK as valuable new Doppler diagnostic criteria for the tardus parvus in CKD too. Data from 183 control patients and 135 chronic kidney disease patients (CKD) were included in the study to test the feasibility of the method and plausibility of the hypothesis. Criteria inclusion was a color Doppler ultrasound measurement of the renal (RRI) and spleen resistive index (SRI). Serum creatinine ( $0.83 \pm 0.20$  vs  $3.27 \pm 1.74$ ), RRI ( $0.60 \pm 0.06$  vs  $0.69 \pm 0.09$ ), SRI ( $0.55 \pm 0.06$  vs  $0.58 \pm 0.09$ ), RISK ( $0.06 \pm 0.04$  vs  $0.11 \pm 0.08$ ), and spleen size ( $94.1 \pm 13.2$  vs  $100.8 \pm 16.5$ ) were higher in CKD patients ( $p < 0.05$ ). RRI correlated with SRI in both groups; however, the coefficient of determination was different ( $Z = 2.29$ ,  $p = 0.022$ ). In the CKD group, RISK correlated inversely with age ( $r = -0.276$ ;  $p = 0.001$ ) and positively with creatinine ( $r = 0.509$ ;  $p < 0.001$ ). In the multivariate analysis, creatinine remained an independent predictor of the high RISK (Wald = 13.07;  $p < 0.001$ ; odds ratio = 1.87; 95% confidence interval 1.33–2.62). Since extraneous factors similarly influence RRI and SRI, the SRI can be considered the correction factor that can estimate the cardiovascular burden on the RRI. Consequently, according to the suggested hypothesis, RISK helps to distinguish the tardus parvus related to RAS from tardus parvus related to systemic influences on Doppler morphology. The identification of the underlying mechanisms of tardus parvus, would help a more accurate characterization of the phenomenon and improve screening and diagnostic test for RAS in CKD patients.

### Introduction

Hypertension has become the most common public health concern worldwide [1] with an estimated overall prevalence of around 30% [2,3]. This disease causes significant morbidity and is an important risk factor for cardiovascular disease events.

The vast majority of high blood pressure diagnoses fall into the category of essential or primary hypertension; however, in some people, a resistant high blood pressure is caused by a condition called secondary hypertension [4]. Among the many potential causes of secondary hypertension, renal artery stenosis (RAS) is an important and

potentially correctable cause [5].

Although the prevalence of RAS is relatively low in patients with mild hypertension [6], the overall prevalence rate is much higher in a highly selected referral population (i.e. malignant hypertension, young patients with hypertension, the presence of an abdominal bruit, decreased serum potassium, unexplained azotemia, recurrent congestive heart failure or flash pulmonary edema [7–12] reaching 20% of patients with end-stage renal failure [13].

Arteriography has been long recognized as the gold standard diagnostic test for the morphologic visualization of RAS [14–16]; however, it is invasive and should not be used as an initial diagnostic test.

\* Address: Policlínica Antônio Ribeiro Netto – Ultrasound Section, Avenida 13 de Maio, 23 – Centro, 20031-902 Rio de Janeiro, RJ, Brazil.

E-mail addresses: [nordeval@oi.com.br](mailto:nordeval@oi.com.br), [nordevalaraujo@gmail.com](mailto:nordevalaraujo@gmail.com).

Doppler ultrasound is recommended as the routine test for detection of RAS in patients with hypertension [17]. Although the Duplex ultrasound offers several advantages, such as wide availability, noninvasiveness, low cost, and patient tolerance, its use as a screening test is still a matter of debate [18,19].

Using Doppler sonography, the diagnosis relies on increased blood velocity through the area of the narrowing of the main renal artery [20] or on the characterization of the post-stenotic tardus parvus (small-amplitude waveform with a prolonged systolic rise) phenomenon in the distal renal artery [21], which has been the subject of controversy [22–25].

The use of Doppler sonography to assess blood velocity has been hampered by a number of factors like obesity, failure to hold the breath, bowel gas, accessory renal arteries, and acoustic shadowing due to calcified plaques, which affect method accuracy [19,24–26]. On the other hand, the uncertainty about the best Doppler parameter to be used for characterization of tardus parvus has yielded the appearance of a variety of studies [22–25].

### Hypothesis

Recently, the difference between the resistive index of the spleen and kidney (DI-RISK) (from now on called RISK) has been proposed as a potential marker of kidney damage [27]. More recently, RISK has been shown to be useful for diagnosis of RAS in patients without chronic kidney disease (CKD) [28]. Based on these assumptions, the hypothesis of this study was to speculate further and propose the RISK as valuable new Doppler diagnostic criteria for the tardus parvus phenomenon in order to improve the diagnosis of RAS in CKD patients too.

### Material and methods

In order to test the feasibility of the method and plausibility of the hypothesis preliminary data from a pilot study was included. The study design was a retrospective survey based on single samples. All patients were referred for sonography evaluation by a group of general practitioners.

The study took place between June 2010 and August 2017 and included 318 subjects, all of whom underwent a standardized investigation of the left kidney and spleen using color Doppler ultrasound in a routine ultrasound examination using the translumbar approach on an outpatient basis [ultrasound section of the Policlínica Antonio Ribeiro Netto, Rio de Janeiro, Brazil].

Participants were excluded from the present analysis due to the presence of morphological kidney abnormalities such as pyelectasia, solid tumors, single kidney, horseshoe kidney, or disparity in renal length larger than 15 mm [26] [if the left kidney was smaller]. Patients undergoing dialysis and patients who received a kidney transplant were ruled out. Patients referred for renal Doppler to rule out RAS were also excluded regardless of the result.

Based on findings of a population-based study (726 subjects) [29], in which reference values for RRI were established [women:  $0.64 \pm 0.05$ ; men:  $0.62 \pm 0.05$ ], patients with RRI less than 0.52 (mean less two standard deviations) were also excluded. Also based on a large series [30,31] using the same criteria, a spleen size larger than 140 mm has been established as the threshold for the definition of splenomegaly and excluded from the study.

Subjects who denied systemic arterial hypertension, diabetes mellitus or cirrhosis and whose renal cortical echogenicity were normal at gray-scale ultrasound were assigned to the healthy control group. In some cases, a serum creatinine determination was also available. Patients whose kidney was more echogenic than the liver or whose serum creatinine was higher than 1.4 mg/dL were assigned to the chronic kidney disease (CKD) group without concern for the underlying disease.

All ultrasounds were performed by the same operator using a

Sonoace 8000SE instrument (Samsung, Seoul, South Korea) with 3.5-MHz transducer. The only parameters that we considered significant for our study according to our baseline hypothesis were spleen and kidney dimensions and resistive indexes. With the patient in the lateral decubitus position, real-time splenic and left kidney examination was performed in both the longitudinal and transverse planes to achieve complete visualization of the organ. First, we measured the longitudinal diameter, which is the maximum length obtained with clearly defined splenic and kidney edges. Then we examined color Doppler flow and spectral Doppler, studying at least two and in most cases three intrasplenic arteries, immediately after they perforated through the organ capsule and intraparenchymal (interlobar or segmental) kidney arteries. The main renal arteries were not scanned.

Measurements were performed with the probe in such a position as to achieve an ultrasound beam nearly parallel to the blood flow direction of the artery (as close as possible to  $0^\circ$ ). The resistive index of the spectra was manually measured with built-in software via the ultrasound scanner. A 2–4-mm spectral gate, no angle correction, and low scale without aliasing were used to sample blood flow velocity.

### Statistical analysis

Results are presented as mean  $\pm$  standard deviation for continuous variables and as a percentage for dichotomous variables. Groups were compared using the Student's *t*-test for continuous variables and Chi-Square tests for categorical variables. Correlations between continuous variables were assessed using the Pearson's test. The significance of the difference between the correlation coefficients of RRI and SRI in controls and CKD patients has been assessed using the Fisher R-to-Z transformation. RISK values were divided into tertiles. The groups (tertiles) were defined by RISK cut-off values reflecting the 33rd and 66th percentiles of the RISK distribution. Multivariate regression analysis evaluated the independent association of variables with the low RISK tertile in comparison to high RISK tertile. Data were analyzed using SPSS software (version 17.0, Chicago, Illinois, USA). Significant differences between groups were indicated by a *p*-value less than 0.05.

The institutional ethics committee approved the study protocol with the waiver of informed consent due to the retrospective nature of the study.

### Results

A total of 318 patients (CKD patients,  $n = 135$  and control subjects,  $n = 183$ ) met the inclusion criteria. All kidneys from the healthy control group were normal at gray-scale ultrasound in terms of shape, echogenicity, localization and size. No kidney had evidence of pyelectasia or solid tumors; stones or cysts without pyelectasia were neglected.

Controls and CKD patients matched in age ( $52.0 \pm 13.0$  vs.  $54.1 \pm 16.0$  years;  $p = 0.184$ ) and sex (male, 45.9% vs 51.9%;  $p = 0.294$ ). Serum creatinine ( $0.83 \pm 0.20$  vs.  $3.27 \pm 1.74$  mg/dL;  $p < 0.001$ ), RRI ( $0.60 \pm 0.06$  vs.  $0.69 \pm 0.09$ ;  $p < 0.001$ ), SRI ( $0.55 \pm 0.06$  vs.  $0.58 \pm 0.09$ ;  $p < 0.001$ ), RISK ( $0.06 \pm 0.04$  vs.  $0.11 \pm 0.08$ ;  $p < 0.001$ ), and spleen size ( $94.1 \pm 13.2$  vs.  $100.8 \pm 16.5$  mm;  $p < 0.001$ ) were higher in CKD patients.

RRI was significantly correlated with SRI in controls and CKD patients as well; however, the difference in the coefficient of determination of these correlations was statistically significant ( $Z = 2.29$ ,  $p = 0.022$ ) (Fig. 1).

The RISK mean value was 0.080 (SD = 0.064) for the whole group. Fourteen out of 318 participants (4.4%) had a RISK value less than zero. Twelve patients were from the healthy control group (6.6%), and two only were from CKD group (1.5%).

In the CKD group, RISK correlated inversely with age ( $r = -0.276$ ;  $p = 0.001$ ) and positively with serum creatinine levels ( $r = 0.509$ ;  $p < 0.001$ ) in univariate analysis. In the multivariate analysis,

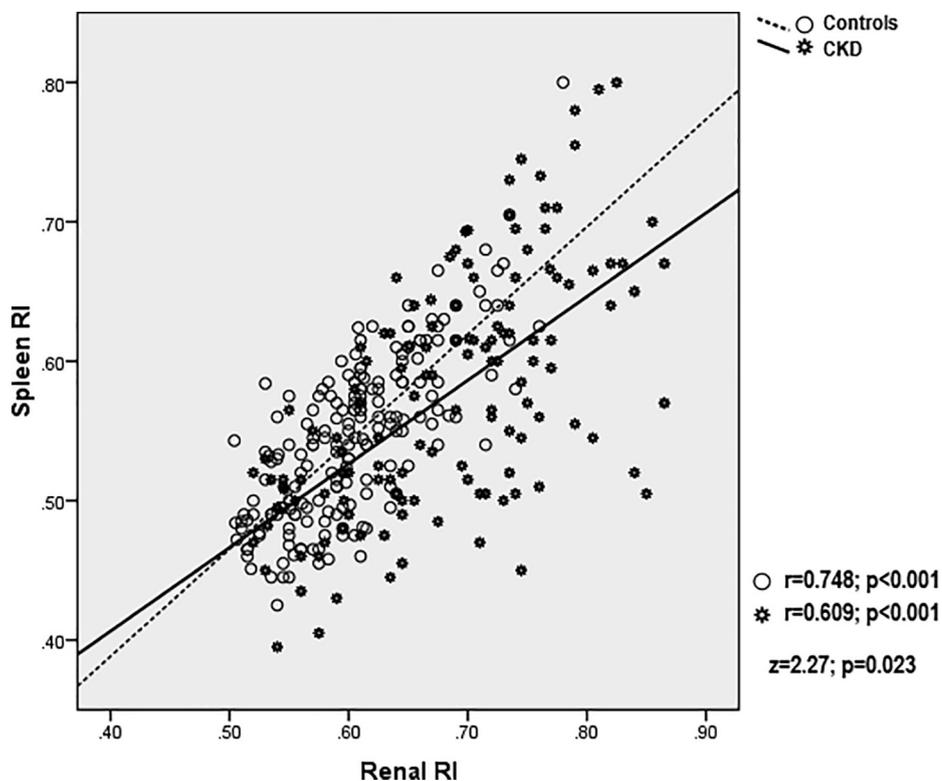


Fig. 1. Correlation between the RRI and SRI in the control and CKD patients. Although the renal and spleen RI have a good relationship in the control and CKD patients, the statistical difference between the coefficient of determination of both correlations (Fisher R-to-Z transformation) demonstrated that every unit of renal RI per spleen RI increment is greater in CKD patients than in the controls.

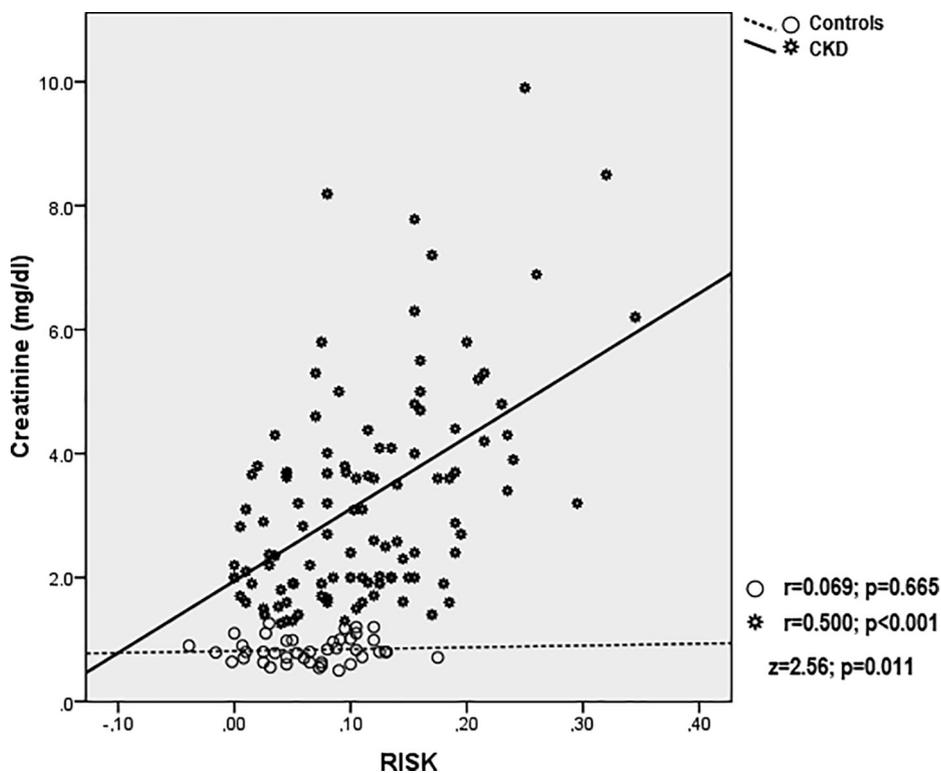


Fig. 2. Correlation between RISK and creatinine levels in the control and CKD patients. There is a conspicuous increase of RISK related to creatinine in CKD patients, whereas the same correlation line in the controls has no slope, an expected finding, since the amplitude of the variation of creatinine levels is negligible in this group.

creatinine remained an independent predictor of the high RISK (Wald = 13.07;  $p < 0.001$ ; odds ratio = 1.87; 95% confidence interval 1.33–2.62). The influence of creatinine on RISK is highlighted in Fig. 2, which depicts the comparison of the correlation between values of RISK and creatinine in controls and CKD patients. No correlation was found

between RISK and age and creatinine in controls ( $r = 0.036$ ,  $p = 0.627$  and  $r = 0.069$ ,  $p = 0.665$ , respectively).

## Discussion

The finding of larger spleens in CKD patients versus controls is in line with studies that reported increased renal size assessed by scintigraphy in patients who were receiving hemodialysis [32] and heavier spleens in patients who underwent a splenectomy in preparation for renal transplantation [33]. To the best of our knowledge, this is the first study describing increased spleen size in CKD patients receiving a conservative treatment. This finding is even more impressive in view of the fact that spleens larger than 140 mm were excluded from analysis (nine from the CKD group and none from controls). However, the reason of this association is beyond the scope of this paper.

Despite the overwhelming majority of patients presenting with elevated blood pressure with no clear etiology and classified as having essential hypertension, the anti-hypertensive therapy can be withdrawn or can often be reduced by performing safe and widely used percutaneous transluminal angioplasty on well-selected patients with RAS, which is the most common cause of secondary hypertension.

Accordingly, an accurate screening diagnosis test is highly desirable in patients with suspected renovascular hypertension to identify who could benefit from early renal artery interventions when treatment may be more successful

## Plausibility of the hypothesis

This study addresses the hypothesis that the difference of resistive indexes in spleen and kidney (RISK) of CKD patients might be used to characterize the intrarenal Doppler tardus parvus phenomenon in RAS as an adjunct to current criteria based on Doppler technique.

In line with the findings of Grün et al. [27], data from the present work showed that CKD patients have higher renal and spleen RI than control subjects. However, renal RI is affected to a higher extent than the spleen RI in CKD patients so that the average RISK is also higher in this group. Indeed, although the renal and spleen RI have a good relationship in the control and CKD patients, the statistical difference between both correlations demonstrated that every unit of renal RI per spleen RI increment is greater in CKD patients than in controls.

This phenomenon probably explains why the RISK in this group has a negative value in only two patients in contrast to 12 cases in the control group. As a consequence, it is reasonable to speculate that a negative RISK value in the CKD group would tip the balance between low RRI and high SRI towards low RRI which would be expected in the case of tardus parvus phenomenon in RAS. Moreover, a lower RISK value based on a high SRI does not seem logical in the current study clinical context [34–36].

One point worth spelling out is why more controls than CKD patients had negative RISK values. It is well known that the renal RI is higher in CKD, mainly due to interstitial and vascular histological changes [37], which would prevent the RISK being negative in almost all cases. In accordance with this study, RISK had a positive correlation with creatinine levels in univariate and multivariate analysis. Since such histological changes are not expected to occur in control subjects, the RRI is more likely to be lower than the SRI, which is a mandatory situation to have RISK negative values. This can be seen as an attribute that makes RISK more specific to mirror tardus parvus in CKD patients, a group well known as more likely to have RAS [13].

Taken together, it is reasonable to hypothesize that low RISK values, mainly negative values, point toward an intrarenal dampened arterial waveform, the pathophysiological basis of the tardus parvus phenomenon. Indeed, low or negative RISK value has been associated angiographically proved RAS in hypertensive patients without CKD [28]. On the other hand, the finding of RISK negative values, in controls and CKD patients without RAS, reported here and by others [27], challenge the cut-off value of  $\leq 0.03$  as indicative for RAS [28].

## Disadvantages of current Doppler parameters

Doppler sonography has been established as a screening tool for detecting RAS. However, one of the drawbacks of using this test is that there are no established standard criteria for differentiating between normal and abnormal Doppler ultrasonographic results. Nonetheless, several published studies on diagnostic Doppler ultrasound have proposed various diagnostic criteria.

Direct evaluation of the main renal artery provides a reliable means of RAS evaluation [38]. However, it is time-consuming, difficult to reproduce, technically difficult in large patients, and limited by individual variability in the course of the main renal artery and by excessive bowel gas or inability to hold the breath [38]. Moreover, the stenosis is a very localized finding, and it necessitates scanning of the entire length of both renal arteries [39].

Indirect evaluation of RAS has emerged as an alternative method of identifying RAS. The rationale is that the flow at the renal hilum downstream to a hemodynamically significant stenosis should become damped and show slowed systolic acceleration with a decreased resistive index designating the tardus parvus effect [40,41].

Diagnostic criteria proposed to characterize tardus parvus phenomenon for the diagnosis of distal stenoses include blunting of early systolic peak acceleration ( $< 3 \text{ m/s}^2$ ), an acceleration index greater than  $4 \text{ m/s}^2$ , an increase in time to systolic peak ( $> 0.07 \text{ s}$ ), or greater than 5% difference in RRI between kidneys [42].

Several articles have shown excellent results with this indirect technique [43,44].

Although such intrarenal parameters can be used as a shortcut to overcome technical demands inherent to main RAS interrogation, they also carry a lot of drawbacks which make them less likely to produce reliable information than a Doppler examination near the emergence of the renal arteries.

Firstly, in patients with atherosclerosis the tardus parvus waveform morphology is less obvious [45]. Secondly, analysis of intrarenal parameters has been shown to be highly reliable for detecting severe stenosis ( $> 75\%$ ) only [46]. Thirdly, patients who are young or have highly compliant arteries may have an absent early systolic peak, which may yield false-positive results [47]. Conversely, noncompliant vessels may not display the tardus parvus response and may result in false-negative results [22]. Fourthly, a drawback of the acceleration time determination has been that there are different remark points according to the waveform [24]. Fifthly, lateralization of the RI values obtained on the two kidneys is considered to be a reflection of unilateral stenosis [41]. However, it does not apply in patients with a solitary kidney or a renal allograft and if the stenosis occurs bilaterally this parameter may produce a false-negative finding [26]. Finally, the appearance of the waveforms is profoundly influenced by several extraneous factors, such as cardiac factors [48], age, use of anti-hypertensive drugs, preexistent parenchymal damage, remodeling of the microcirculation (atherosclerotic disease, hypertension, and diabetes), valvular heart disease, left ventricular contractility disorders and heart rate [43], and may make the test nonspecific.

## Advantage of RISK parameter

Because of the above-mentioned disadvantages of the current criteria for characterization of the tardus parvus phenomenon, the proposal of new diagnostic criteria, even though it is in the step of knowledge creation, should be taken into consideration to improve practice guidelines for the diagnosis of RAS in CKD patients. Moreover, the resistive index is the most common Doppler parameter, and it is widely used and easier to calculate than systolic acceleration time.

A common criticism of the renal RI diagnostic criteria value has been that it reflects more the systemic cardiovascular burden and does not capture intrinsic renal abnormalities [49].

One can speculate that a possible solution to overcome these

problems is a variable that would be able to help this situation by resolving or reducing the effect of extraneous factors on tardus parvus phenomenon interpretation.

Since cardiovascular factors and systemic atherosclerotic disease influence similarly renal and splenic RI, the splenic RI can be considered the correction factor that estimates the cardiovascular burden on renal RI [27]. Consequently, the effects of extraneous factors did not lead to any detectable change in the RISK, and the difference between renal and splenic RI can be interpreted as a more specific marker of renal disease [27].

Using the same principle, it is therefore reasonable to speculate that RISK has the potential to neutralize the impact of extraneous factors (since they would affect simultaneously renal and splenic RI) on the analysis and interpretation of renal RI, and consequently, to use lower values as indicative of RAS. Indeed, that has already been shown in hypertensive patients without CKD [28].

Inspired by the rationale behind RISK, the aim of the present study was to provide a theoretical basis for the development of a new Doppler diagnostic parameter for distinguishing the tardus parvus phenomenon related to RAS from tardus parvus related to systemic influences on Doppler morphology of intrarenal arteries in CKD patients too.

Of course, the most important limitation of the present study is that it has not been carried out in a clinical setting for which the diagnostic criteria had been proposed. Therefore, the data obtained in this investigation are not appropriate for the assessment of certain types of statistical analysis, such as sensitivity, specificity, and negative and positive predictive values. The attention was limited to differences in RISK values between the controls and CKD patients without RAS assuming that lower values could be associated with the tardus parvus phenomenon in case of RAS. Accordingly, as an effort to exclude RAS cases, it was decided to exclude all patients who had been referred for RAS screening, cases of asymmetrical kidney size (if left kidney was the smaller), or a Doppler sonogram that shows the classic appearance of a tardus parvus waveform in order to study a well-defined group of control and CKD patients without well-known findings related to renovascular hypertension. In addition, based on a large study population [30], patients with an RRI lower than mean less two standard deviations, have also been excluded, since subjects with a low RRI carry the chance of having attributes that will make it possible to have tardus parvus. However, since no participant has been further studied to rule out RAS, it is not possible to exclude the likelihood that any patient has contaminated the sample.

Although further confirmations are needed, this method poses the potential to enhance the current conventional Doppler diagnosis criteria for RAS in CKD patients too. On the basis of data from this preliminary study combined with the conclusions of previous reports, it is reasonable to believe that researchers studying the value of the duplex ultrasound for renal artery disease should test RISK as criteria for tardus parvus in CKD patients. Therefore, it might be important to determine how these criteria perform in appropriate clinical situations in different centers.

In conclusion, RISK might be useful as an adjunct to refine the Doppler technique for characterization of the tardus parvus phenomenon and to improve screening and diagnostic tests for RAS in CKD patients. It would be valuable to assess this variable in the appropriate clinical setting to evaluate its applicability to clinical practice. Further studies carried out in the appropriate clinical framework are needed to determine the diagnostic value of RISK in comparison to gold standard methods.

#### Conflict of interest

I declare that I have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.01.016>.

#### References

- [1] Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005;365:217–23.
- [2] Gillespie CD, Hurvitz KA. Prevalence of hypertension and controlled hypertension—United States, 2007–2010. *MMWR Suppl* 2013;62:144–8.
- [3] Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. *JAMA* 2003;290:199–206.
- [4] Rudnick KV, Sackett DL, Hirst S, Holmes C. Hypertension in a family practice. *Can Med Assoc J* 1977;117:492–7.
- [5] Dieter RS. The functional assessment of renal artery stenosis. *Expert Rev Cardiovasc Ther* 2005;3:369–70.
- [6] Hansen KJ, Edwards MS, Craven TE, et al. Prevalence of renovascular disease in the elderly: a population-based study. *J Vasc Surg* 2002;36:443–51.
- [7] Bloch MJ, Basile J. The diagnosis and management of renovascular disease: a primary care perspective. *J Clin Hypertens* 2003;5:261–8.
- [8] Strandness DE. Doppler and ultrasound methods for diagnosis. *Sem Nephrol* 2000;20:445–9.
- [9] Harding MB, Smith LR, Himmelstein SI, et al. Renal artery stenosis: prevalence and associated risk factors in patients undergoing routine cardiac catheterization. *J Am Soc Nephrol* 1992;2:1608–16.
- [10] Zierler RE, Bergelin RO, Polissar NL, et al. Carotid and lower extremity arterial disease in patients with renal artery atherosclerosis. *Arch Int Med* 1998;158:761–7.
- [11] Svetkey LP, Basile J, Dunnick NR, et al. Similar prevalence of renovascular hypertension in selected blacks and whites. *Hypertension* 1991;17:678–83.
- [12] Setaro JF, Saddler MC, Chen CC, et al. Simplified captopril renography in diagnosis and treatment of renal artery stenosis. *Hypertension* 1991;18:289–98.
- [13] Mailloux LU, Napolitano B, Belkicci AG, Vernace M, Wilkes BM, Mossey RT. Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes: a 20 year clinical experience. *Am J Kidney Dis* 1994;24:622–9.
- [14] Hillman BJ. Imaging advances in the diagnosis of renovascular hypertension. *Am J Roentgenol* 1989;153:5–14.
- [15] Safian RD, Textor SC. Renal-artery stenosis. *N Engl J Med* 2001;344:431–42.
- [16] Haller C. Arteriosclerotic renal artery stenosis: conservative versus interventional management. *Heart* 2002;88:193–7.
- [17] Williams GJ, Macaskill P, Chan SF, et al. Comparative accuracy of renal duplex sonographic parameters in the diagnosis of renal artery stenosis: paired and unpaired analysis. *Am J Roentgenol* 2007;188:798–811.
- [18] Zierler RE. Is duplex scanning the best screening test for renal artery stenosis? *Semin Vasc Surg* 2001;14:177–85.
- [19] Rabbia C, Valpreda S. Duplex scan sonography of renal artery stenosis. *Int Angiol* 2003;22:101–15.
- [20] Postma CT, van Aalen J, de Boo T, Rosenbusch G, Thien T. Doppler ultrasound scanning in the detection of renal artery stenosis in hypertensive patients. *Br J Radiol* 1992;65:857–60.
- [21] Radermacher J, Chavan A, Schäffer J, et al. Detection of significant renal artery stenosis with color Doppler sonography: combining extrarenal and intrarenal approaches to minimize technical failure. *Clin Nephrol* 2000;53:333–43.
- [22] Bude RO, Rubin JM, Platt JF, Fechner KP, Adler RS. Pulsus tardus: its cause and potential limitations in detection of arterial stenosis. *Radiology* 1994;190:779–84.
- [23] Grataloup-Oriez C, Plainfosse MC, Challande P, et al. Renal artery stenosis detection in 123 hypertensive patients comparison between Doppler and angiography. *Eur J Ultrasound* 1997;5:155–63.
- [24] Kliever MA, Tupler RH, Carroll BA, et al. Renal artery stenosis: analysis of Doppler waveform parameters and tardus-parvus pattern. *Radiology* 1993;189:779–87.
- [25] Ripolles T, Aliaga R, Morote V, et al. Utility of intrarenal Doppler ultrasound in the diagnosis of renal artery stenosis. *Eur J Radiol* 2001;40:54–63.
- [26] Schwerk WB, Restrepo IK, Stellwaag M, Klose KJ, Schade-Brittinger C. Renal artery stenosis: grading with image directed Doppler US evaluation of renal resistive index. *Radiology* 1994;190:785–90.
- [27] Grün OS, Herath E, Weihrauch A, et al. Does the measurement of the difference of resistive indexes in spleen and kidney allow a selective assessment of chronic kidney injury? *Radiology* 2012;264:894–902.
- [28] Grupp C, Koziolok MJ, Wallbach M, et al. Difference between renal and splenic resistive index as a novel criterion in Doppler evaluation of renal artery stenosis. *J Clin Hypertens* 2018;20(3):582–8.
- [29] Ponte B, Pruijm M, Ackermann D, et al. Reference values and factors associated with renal resistive index in a family-based population study. *Hypertension* 2014;63:136–42.
- [30] Hosey RG, Mattacola CG, Kriss V, Armsey T, Quarles JD, Jagger J. Ultrasound assessment of spleen size in collegiate athletes. *Br J Sports Med* 2006;40:251–4.
- [31] Spielmann AL, DeLong DM, Kliever MA. Sonographic evaluation of spleen size in tall healthy athletes. *Am J Roentgenol* 2005;184:45–9.

- [32] Platts MM, Anastassiades E, Sheriff S, Smith S, Bartolo DC. Spleen size in chronic renal failure. *Br Med J* 1984;289:1415–8.
- [33] George CR, Tremann JA, Quadracci LJ, Striker GE, Marchioro TL. The spleen in chronic renal failure and renal transplantation. *Proc Clin Dial Transplant Forum* 1972;2:1–4.
- [34] Corradi F, Brusasco C, Garlaschi A, et al. Splenic Doppler resistive index for early detection of occult hemorrhagic shock after polytrauma in adult patients. *Shock* 2012;38:466–73.
- [35] Bolognesi M, Sacerdoti D, Merkel C, et al. Splenic Doppler impedance indices: influence of different portal hemodynamic conditions. *Hepatology* 1996;23:1035–40.
- [36] Byun JN, Kim DH. The value of renal artery resistive indices: association with esophageal variceal bleeding in patients with alcoholic cirrhosis. *J Korean Radiol Soc* 2007;56:355–60.
- [37] Bigé N, Lévy PP, Callard P, et al. Renal arterial resistive index is associated with severe histological changes and poor renal outcome during chronic kidney disease. *BMC Nephrol* 2012;13:139.
- [38] Desberg AL, Paushter DM, Lammert GK, et al. Renal artery stenosis: evaluation with color Doppler flow imaging. *Radiology* 1990;177:749–53.
- [39] Kohler TR, Zierler RE, Martin BS, et al. Noninvasive diagnosis of renal artery stenosis by ultrasonic duplex scanning. *J Vasc Surg* 1986;4:450–6.
- [40] Handa N, Fukunaga R, Ogawa S, Matsumoto M, Kimura K, Kamada T. A new accurate and non-invasive screening method for renovascular hypertension: the renal artery Doppler technique. *J Hypertens Suppl* 1988;6:S458–60.
- [41] Stavros AT, Parker SH, Yakes WF, et al. Segmental stenosis of the renal artery: pattern recognition of tardus and parvus abnormalities with duplex sonography. *Radiology* 1992;184:487–92.
- [42] Lao D, Parasher PS, Cho KC, Yeghiazarians Y. Atherosclerotic renal artery stenosis – diagnosis and treatment. *Mayo Clin Proc* 2011;86:649–57.
- [43] Meola M, Petrucci I. Color Doppler sonography in the study of chronic ischemic nephropathy. *J Ultrasound* 2008;11:55–73.
- [44] Krumme B. Renal Doppler sonography – Update in clinical nephrology. *Nephron Clin Pract* 2006;103:c24–8.
- [45] Demirpolat G, Ozbek SS, Parildar M, Oran I, Memis A. Reliability of intrarenal Doppler sonographic parameters of renal artery stenosis. *J Clin Ultrasound* 2003;31:346–51.
- [46] Gottlieb RH, Hartley DF, Rubens DJ, et al. Effect of a main renal artery stenosis on the downstream Doppler waveform in dogs. *Acad Radiol* 1995;2:768–75.
- [47] Halpern EJ, Deane CR, Needleman L, Merton DA, East SA. Normal renal artery spectral Doppler waveform: a closer look. *Radiology* 1995;196:667–73.
- [48] Wood MM, Romine LE, Lee YK, et al. Spectral Doppler signature waveforms in ultrasonography: a review of normal and abnormal waveforms. *Ultrasound Q* 2010;26:83–99.
- [49] Seiler S, Colbus SM, Lucisano G, et al. Ultrasound renal resistive index is not an organ-specific predictor of allograft outcome. *Nephrol Dial Transplant* 2012;27:3315–20.