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IM - REVIEW

The internist and the renal resistive index: truths and doubts

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Abstract The renal resistive index (RRI) is measured by Doppler sonography in an intrarenal artery, and is the difference between the peak systolic and end-diastolic blood velocities divided by the peak systolic velocity. The RRI is used for the study of vascular and renal parenchymal renal abnormalities, but growing evidence indicates that it is also a dynamic marker of systemic vascular properties. Renal vascular resistance is only one of several renal (vascular compliance, interstitial and venous pressure), and extrarenal (heart rate, aortic stiffness, pulse pressure) determinants that combine to determine the RRI values, and not the most important one. RRI cannot always be considered a specific marker of renal disease. To summarize from the literature: (1) hydronephrosis, abdominal hypertension, renal vein thrombosis and acute kidney injury are all associated with an acute increase in interstitial and venous pressure that determine RRI values. In all these conditions, RRI is a reliable marker of the severity of renal damage. (2) The hemodynamic impact of renal artery stenosis can be assayed by the RRI decrease in the homolateral kidney by virtue of decreasing pulse pressure. However, renal diseases that often coexist, increase renal vascular stiffness and hide the hemodynamic effect of renal stenosis. (3) In transplant kidney and in chronic renal disease, high RRI values (>0.80) can independently predict renal and clinical outcomes, but systemic (pulse pressure) rather than renal hemodynamic determinants sustain the predictive role of RRI. (4) Higher RRI detects target renal organ damage in hypertension and diabetes when renal function is still preserved, as a marker of systemic atherosclerotic burden. Is this the fact? We attempt to answer.

Keywords Renal resistive index · Ultrasound · Renal disease · Pulse pressure · Arterial stiffness

Introduction

The renal resistive index (RRI), derived from the Doppler spectrum of intrarenal (segmental interlobar) arteries, is obtained by the difference between maximum and minimum (end-diastolic) flow velocity to maximum flow velocity (Fig. 1): RRI = (maximum velocity − minimum velocity) maximum velocity. The RRI was introduced in 1950, and was initially proposed for the semiquantitative assay of intra-renal vascular resistance by Gosling and Pourcelot in 1974, who showed that the ratio was influenced by changes in vascular resistance distal to the point of RRI assay [1].

According to these findings, RRI was used for the diagnosis and follow-up of acute and chronic renal disease [2] that are associated with dynamic or structural changes in intra-renal vessels, and in the following years, RRI was considered a strong independent predictor of renal failure [3]. However, in the meantime, growing evidence was collected that RRI has many intra and extra-renal determinants, that renal vascular resistance is only one of these, and not the most important (Fig. 2). Remarkably, in 1991 Gosling et al. [4] and in 1999 Bude and Rubin [5] clearly show by in vitro experiments performed in simple artificial

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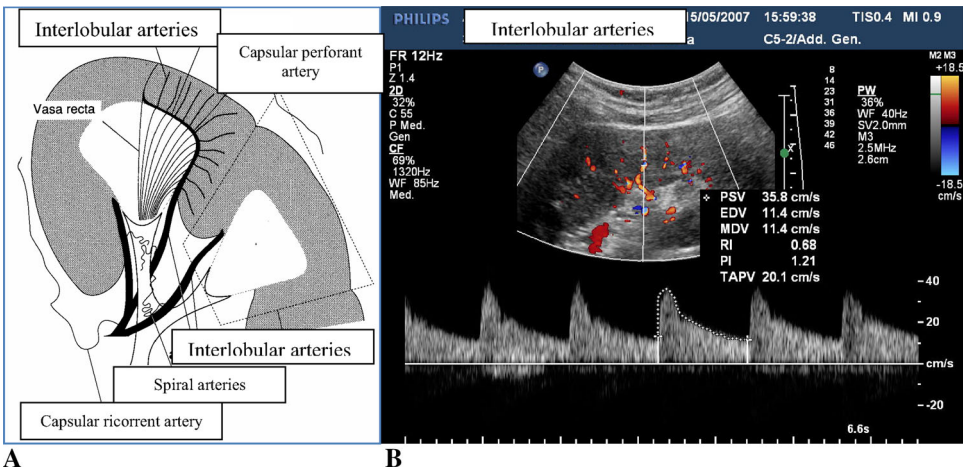

Fig. 1 **a** Schematic anatomic topography of interlobar arteries in the renal cortex. **b** The renal resistive index (RRI) is measured by Doppler sonography in an intrarenal interlobar artery, and is the difference between the peak systolic (PSV) and end-diastolic (EDV) blood velocities divided by the peak systolic velocity (PSV)

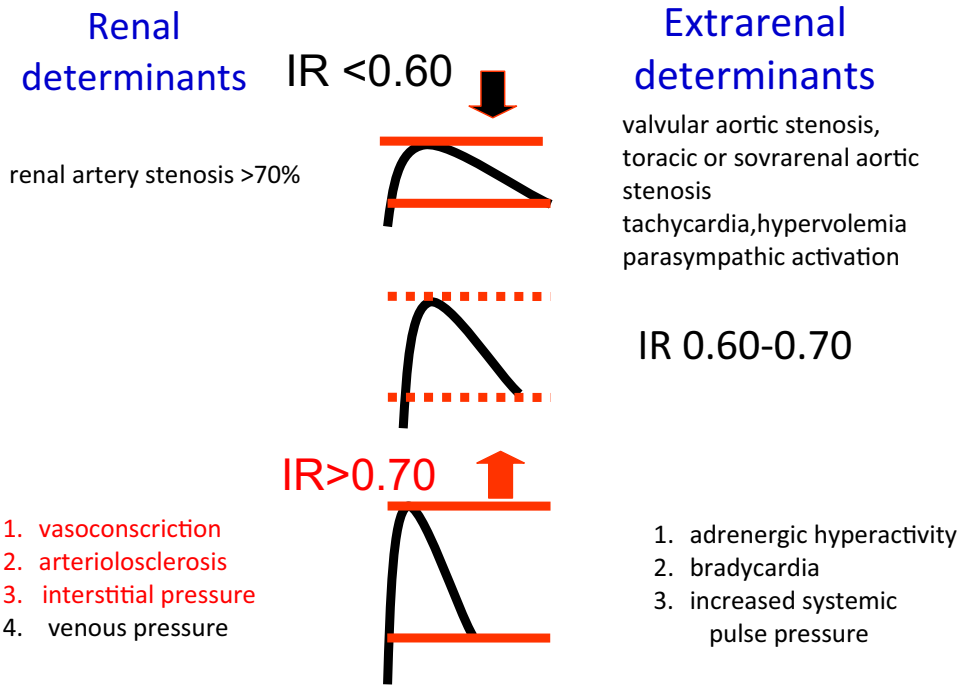

Fig. 2 Different renal and extrarenal determinants concur to determine RRI

circuits that RRI is dependent on both renal vascular compliance and resistance, becoming less dependent on resistance as compliance decreases. Moreover, experimental and clinical data prove that RRI is scarcely influenced by renal vascular resistance, and markedly affected by renal (renal interstitial and venous pressure) and systemic (aortic stiffness, pulse pressure) determinants [6]. In vivo, pulse pressure is influenced primarily by extrarenal factors, specifically cardiac function and systemic arterial compliance that is affected by age and traditional cardiovascular (CV) risk factors [7]. Evidence was collected that in chronic renal diseases and in transplant recipients, RRI mainly depends on systemic vascular compliance rather than on renal vascular properties. According to this point of view, in these patients, RRI predicts renal and general outcomes, as a marker of atherosclerotic burden rather than being a marker of renal damage. However, this statement is still a matter of debate.

On the contrary, full agreement was reached on the clinical use of RRI as a specific marker of renal damage, in subjects affected by renal pathologies: i.e., hydronephrosis, renal vein thrombosis, increased abdominal pressure and acute kidney injury, which cause an acute increase in renal interstitial or venous pressure.

The aim of this review is to give information about the knowledge of pathophysiologic renal and extra-renal determinants of RRI, necessary for the correct use of RRI ultrasound measurement in clinical practice. Specifically,

clinical pathologies in which the RRI must be considered as a specific marker of renal damage are described in detail, and differentiated from those in which renal and systemic vascular parameters concur to modify RRI, and the role of RRI as an independent predictor of general and renal outcome is debated.

Systemic and renal determinants of RRI

Systemic pulse pressure and aortic stiffness

The ratio of diastolic to systolic blood pressure (see RRI equation) is an inverse function of pulse pressure. So, for any given intra-renal vascular resistance, an increase in systolic arterial pressure increases and promotes a greater peak renal velocity or a decrease in diastolic arterial pressure that results in a lower end-diastolic velocity (Fig. 3). As a direct consequence, the increase in systemic arterial stiffness causes an increased pulse pressure, and is associated with high RRI values both in physiological (aging) and pathological (hypertension) conditions. The risk of microvascular damage associated with excessive aortic stiffness is systemic, but low vascular impedance of obligate high-flow organs, such as brain and kidneys, predispose them to pulsatile damage [8]. Changes in pulse pressure can also be tonic or phasic as during an infusion of L-NG-monomethyl arginine (L-NMMA), an inhibitor of endothelial NOS. In these subjects, neither baseline nor the changes in RRI during infusion are related to renal vascular resistance or renal perfusion, assessed with para-amino-hippuric acid and insulin clearance [9]. Remarkably, RRI is related to central pulse pressure and aortic stiffness.

The relationship between RRI and pulse pressure was investigated in recipients of kidney transplants where pulse pressure is clearly recipient specific, and the interlobular arteries are donor specific. In these subjects, RRI correlates with the age of the recipient, but not the donor, with recipient pulse pressure, but not parameters of allograft function, and with the RRI of other (i.e., splenic) districts of the recipient. Moreover, RRI is not related to glomerular, tubular and interstitial pathology of the transplanted kidneys. These results in transplant recipients strongly support that RRI primarily reflects the properties of the systemic vasculature rather than the effects of intrinsic renal damage.

Pulse wave velocity (PWV), which is an indirect measure of aortic stiffness, is a major determinant of pulse pressure, and has been shown to be associated with renal microvascular damage [10]. In hypertensive patients with normal renal function or with chronic renal disease, RRI is significantly associated with aortic PWV independently of renal function [11]. Using arterial tonometry, iohexol clearance and magnetic resonance imaging, Woodard et al. show that in subjects with mean systolic BP in a hypertensive range, and with reduced GFR in 40 % of participants, a stiffer aorta leads to increased delivery of pulsatile energy to the kidneys, resulting in microvascular

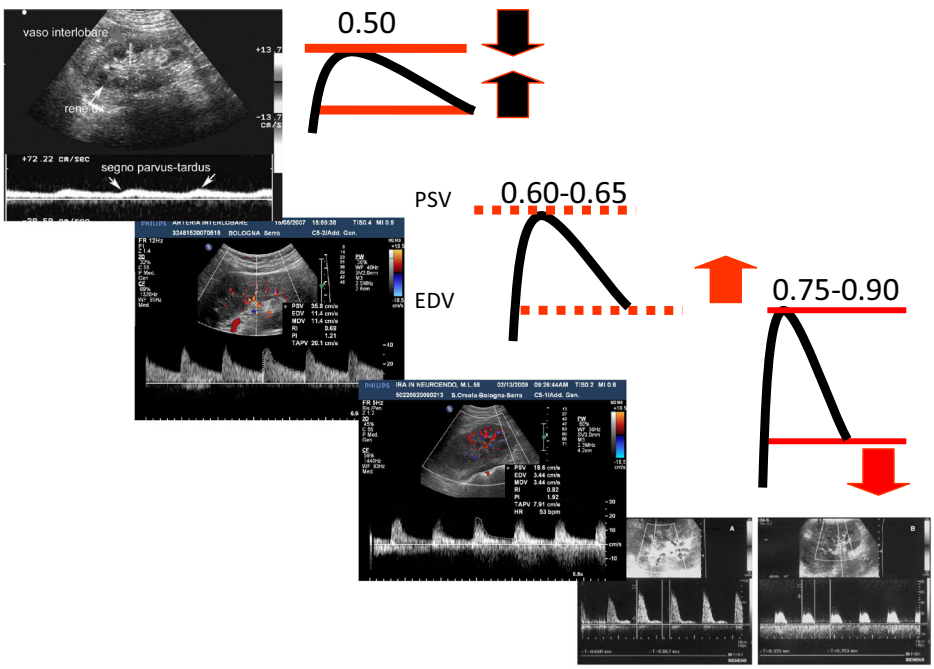

Fig. 3 Schematic representation of RRI changes. From the left to the right: *1*) low RRI values (0.50) because of low peak systolic velocity (PSV) with peculiar Doppler wave pattern of post-stenotic flow characterized by a "tardusslow", and "parvuslittle pulsus"; Doppler wave pattern in the homolateral kidney to >60 % renal artery stenosis, *2*) normal Doppler wave pattern and PSV/EDV at interlobar arteries in healthy control subjects; *3*,*4*) high RRI (0.75–0.90) due to high peak systolic (PSV) and decreased end-diastolic velocity (EDV). Doppler wave pattern in chronic kidney disease or acute kidney injury

rarefaction, increased renal vascular resistance, and reduction in GFR. Understanding of the mechanisms that regulate the relationship between large arteries and the renal microcirculation might lead to new strategies to protect the kidneys from the increased blood pressure load owing to systemic hypertension [12].

Accordingly, a tight relationship between RRI and other markers of atherosclerotic burden, as intima-media thickness and ankle brachial index, is demonstrated in patients with chronic renal disease.

Renal pulse pressure distal to artery stenosis

Severe (>80 %) renal artery stenosis is associated with a decrease in pulse pressure in the vascular tree distal to the stenosis, and decreases RRI values (<0.60) because of low peak systolic velocity. The dampened flow is revealed by the peculiar Doppler waveform pattern characterized by "tardus," slow, and "parvus," weak pulses. The gradual reduction, up to 40 %, of the perfusion pressure does not substantially change renal blood flow and glomerular filtration rate, thanks to the self-regulating mechanisms of intrarenal circulation. This self-control mechanism becomes ineffective when the perfusion pressure falls >40 %, and the systolic pressure is <70–80 mmHg [13]. There is experimental evidence that a fall of 40 % in renal perfusion pressure is realized when morphological renal artery stenosis is >75 %, [14] and it is defined as hemodynamically significant because it activates the renal renin angiotensin system [15]. In these conditions, the findings of the low and asymmetric RRI distal to stenosis provide indirect but reliable evidence of the hemodynamic impact of that renal artery stenosis on the kidney. However, when distal vascular disease is concurrent due to chronic ischemic kidney or nephropathies, this increases the RRI and hides the hemodynamic effects of renal artery stenosis. In these patients, the RRI is symmetrically high, and the hemodynamic effect of arterial stenosis on renal parenchyma cannot be evaluated by Doppler ultrasound.

According to the same hemodynamic mechanism, decreased pulse pressure distal to the stenosis, severe aortic valve stenosis, and stenosis of the thoracic or supra-renal abdominal aorta all decrease RRI. In these patients, RRI is low (<0.60), but symmetric, and no renal artery stenosis is found.

Heart rate

Changes in heart rate can affect RRI independently of the other hemodynamic parameters because of changes in diastolic duration that affect end-diastolic velocity. During bradycardia, diastolic duration increases, and high RRI values are measured. On the contrary, during tachycardia, diastolic duration shortens, and RRI decreases [7].

Renal determinants

Renal interstitial and venous pressure

The renal capillary wedge pressure (interstitial tissue plus venous pressure) is a major renal determinant of RRI. In an ex vivo rabbit kidney model, elevations in ureteral pressure are significantly correlated with increased RRI values, mean renal vascular resistance (pressure/flow), and decreased mean conductance (flow/pressure) [16]. In humans in vivo, the acute increase of renal interstitial pressure by hydronephrosis or of venous pressure by venous thrombosis, or of both by abdominal hypertension, results in a linearly related increase in RRI. Also a renal hematoma can acutely increase the pressure of interstitial compartment.

Most importantly, acute kidney injury (AKI) is associated with an acute increase in interstitial pressure because of ischemic and inflammatory damage of the tubulo-interstitial compartment by sustained hypoperfusion. In all these clinical conditions, the occurrence, severity and progression of renal damage can be well monitored by the changes in RRI values (see dedicated paragraphs).

Histological renal parameters- RRI and the tubulo-interstitial compartment

Twenty years ago, Platt et al. showed that RRI is significantly higher in nephropathies with tubulo-interstitial or vascular injury than in isolated glomerulopathies [17].

Nephropathies characterized by prevalent glomerular involvement only slightly affect RRI; glomerular arterial resistance, which accounts for about 20 % of total renal vascular resistance, has a minor, but still important role in the determination of RRI.

In subsequent years, the studies on the relationship between histological findings and RRI in renal disease and kidney transplants find conflicting results. According to Ikee et al. only arteriolosclerosis out of all histological parameters independently correlates with RRI in chronic renal disease, whereas in renal transplants investigated at 3, 12 and 24 months after transplantation, RRI is not associated with renal allograft histological features [18, 19]. In another study performed in patients with renal parenchymal disease, RRI correlates in order of significance with the degree of arteriolosclerosis, glomerular sclerosis, arteriosclerosis, edema and focal interstitial fibrosis [20]. Moreover, in 202 chronic kidney disease patients who

underwent renal biopsy, Hanamura et al. find a significant association of RRI with glomerulosclerosis, arteriolosclerosis, and tubulo-interstitial damage [21]. On the contrary, other authors report that high RRI values are related to more severe tubulo-interstitial damage scores, and an association between RRI values and the extension of interstitial fibrosis is shown, probably due to the elevation of pressure exerted by interstitial fibrosis on adjacent vessels. Remarkably, interstitial fibrosis closely correlates to renal function and long term prognosis, and may underlie the role of RRI as an independent marker of renal and clinical outcome in chronic renal diseases [22]. In a recent large study involving 952 patients, the RRI correlates with a number of histological parameters, including the glomerulosclerosis score, even if the most evident is observed with the tubulo-interstitial score [23].

The possible use of RRI as a marker of tubulo-interstitial nephropathy is supported by the findings that the detection of high RRI values allows the early identification of both normotensive and hypertensive patients with chronic tubulo-interstitial nephropathy diagnosed by 99mTc DMSA scintigraphy and signs of tubular dysfunction, when renal function is still preserved [24]. Moveover, in hypertensive patients with normal creatinine clearance and no albuminuria, high RRI values are associated with low grade inflammation (Protein C reactive >2 mg/dl) and hyperuricemia (>6.5 mg/dl) [25, 26]. Both sustain a tubulo-interstitial nephropathy. Tubulo-interstitial nephropathies affect the RRI; glomerular nephropathies have a minor but important role in affecting the RRI.

Role of arterial vascular resistance; the great doubt

Based on early experimental animal data, RRI was long considered to directly mirror intrarenal resistance, thus allowing a non-invasive glimpse into intrarenal (patho) physiology [27, 28]. Under physiological conditions, RRI assay can detect phase increase in renal vascular resistance induced by sympathetic activation obtained by a cold pressor test or handgrip. In the same subjects, the increase in blood volume by acute hydration results ed in a decrease in RRI [29]. Repeated daily sessions of music-guided slow-breathing increases parasympathetic modulation, and decreases RRI early in the study. These changes are followed by a positive modulation of baroreflex sensitivity and blood pressure reduction [30]. In patients with heart failure, high RRI values are associated with an increased intrarenal vascular resistance due to neurohormonal hyperactivity, and independently predict heart failure progression [31]. Catheter-based renal sympathetic denervation in patients with resistant hypertension, reduces RRI probably through a reduction in intraparenchymal resistance, not mediated by reduction in systolic blood pressure [32]. As a whole, these findings support the position that RRI can detect phase changes in renal vascular resistance.

However, RRI changes during dynamic vasodilatation caused by nitroglycerin or (L-NMMA) infusion are poorly associated with the contemporaneous direct measurement of renal resistance by scintigraphy, even if the changes in RRI and in renal vascular resistance change in the same direction. Rather, RRI changes are correlated with pulse pressure [7]. For many years, the role of high RRI values as an independent marker of renal outcome in chronic kidney disease was attributed, above all, to the assumption that RRI increase was mainly determined by the progressive increase in vascular resistance owing to : (1) decrease in arterial compliance and increase in vascular resistance due to renal arteriosclerosis; (2) elevation of pressure exerted by interstitial fibrosis in adjacent vessels; (3) vasoconstriction secondary to hypoxia and through loss of capillaries associated with renal fibrosis. All these changes are associated with renal function decline.

During recent years, the evidence suggests that RRI is an independent marker of renal and cardiovascular outcomes because it measures systemic and not renal hemodynamic parameters, and reflects systemic vascular disease [3, 7, 33, 34] (see "Systemic determinants-pulse pressure").

What is the message? RRI is not a measure of renal vascular resistance, and we agree with the title of O'Neill's review "Renal resistive index. A case of mistaken identity" [7]. However in our opinion, there is no doubt that both phasic (sympathetic activation) and tonic (arteriolosclerosis) changes in renal arterial resistance can modulate RRI. Rather doubts persist about the role of RRI as an organ-specific predictor of renal and cardiovascular outcomes.

Which RRI threshold should be use in clinical practice?—the role of age and gender

An increase of RRI with age is described, and is related to the small vessel changes and reduced characteristics of an aging kidney due to arteriosclerosis with increased thickness of the tunica media and reduction of the lumen and fibrosis [29, 35] (Fig. 4). A role of age-related increase in systemic arterial stiffness probably contributes to the progressive increase in RRI. The steep age-dependent rise in the resistive index is specific to renal vasculature, and is not seen in other vascular beds. Most authors use >0.70 as the cut-off to consider RRI values as pathological without establishing normal values according to age. In a recent large multicentric family-based population study, age is confirmed as a determinant of RRI, and also shows that the relationship of RRI with age is nonlinear, and that RRI increases sharply after 40 years of age. For instance, the

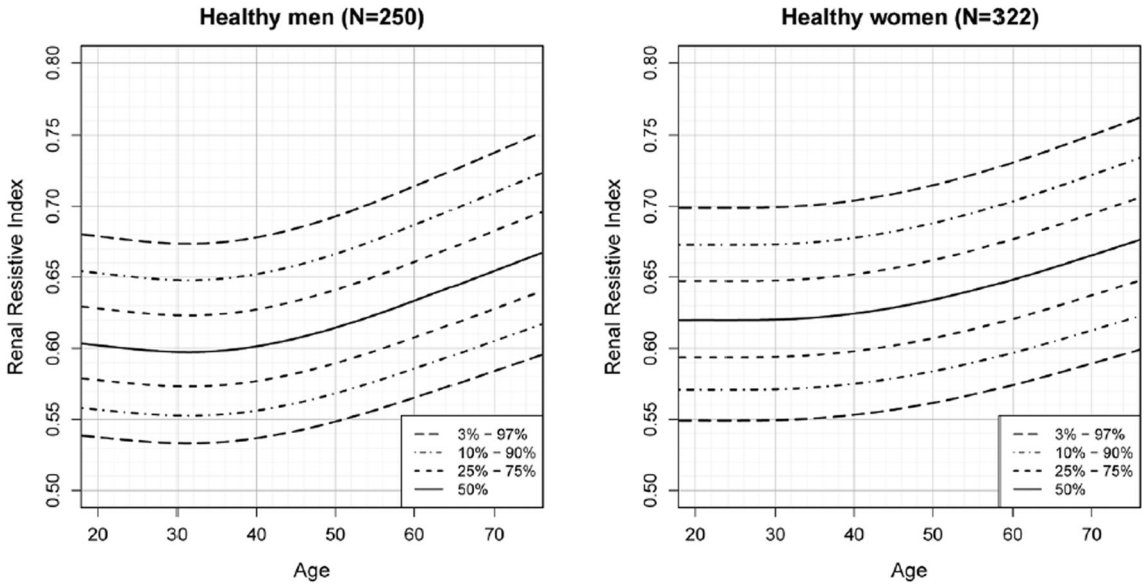

Fig. 4 Normogram of renal resistive index according to age and gender in nondiabetic, nonhypertensive, and non-CKD (healthy) participants ($n = 572$). *CKD* indicates chronic kidney disease [35]

97th percentile among nondiabetic, nonhypertensive, and non-CKD subjects presented in Fig. 4 [35] might serve as a suitable cutoff.

In the same multicentric study, female gender is associated with higher RRI values, perhaps due to hormone differences and the fact that RRI has a heritable trait [35]. The clinical relevance of these findings must be investigated by specific studies.

On the basis of data available in the literature, we strongly suggest that RRI threshold values other than 0.70 might be appropriate depending on the age of investigated patients.

The renal volume to resistive index ratio

Serial measurement of renal volume could be important for evaluating patients with renal disease because changes in renal size might indicate irreversible renal damage. As preclinical chronic ischemia ensues, kidney vascular impedance increases and kidney size becomes smaller. Therefore, the renal volume to resistive index ratio might be a better indicator of intrarenal atherosclerosis than RRI [33].This integration of ultrasound and Doppler findings might help to identify patients with preclinical renal damage, characterized by reduced renal volume and increased renovascular impedance [36]. Renal length and volume combined with resistive index assays appear to be predictive of the specific therapeutic response after percutaneous angioplasty [37]. In the context of long standing hypertension, microalbuminuria and the reduction of renal volume may signal reduced renal flow and increased renovascular resistance [33].

Experimental studies report that renal enlargement precedes renal hyperfunction in the early phase after the onset of experimental diabetes [38]. In humans, renal hypertrophy and the increase in the RRI may represent two different phases of diabetic nephropathy: renal enlargement is a prealbuminuric reversible step of renal damage, whereas the RRI increase indicates the progression of disease with renal scarring, which precedes the appearance of albuminuria [38]. Finally, a lower renal volume to resistive ratio is an independent predictor of diabetes onset in hypertensive patients [39]. The renal volume to resistive index ratio integrates the RRI assay, and can anticipate the preclinical renal damage in chronic (low volume) and diabetic (high volume) nephropathy.

The truths-RRI as specific marker of renal damage

RRI and hydronephrosis

The application of RRI to the diagnosis of acute urinary obstruction was first suggested by Platt in 1989 [40]. An acute unilateral RRI increase associated with hydronephrosis, which is detected 6-48 h from the onset of symptoms, allows the diagnosis of obstructive uropathy [41]. The increase in RRI values is time-dependent, and in patients with long standing hydronephrosis, it can be absent. The accuracy of RRI assay rises to 94 % when the RRI is higher than 0.7, the inter-renal RRI difference is

greater than 0.08–0.1 or higher than 10 %, and the ureteral jet is asymmetrically absent or reduced [40, 42]. The inter-renal RRI difference (Delta RI) is associated with the severity of obstruction shown by intravenous pyelography. The highest Delta RI (0.116 ± .030) is found in patients with functional exclusion of the kidney [43]. An accuracy of 94 % and a specificity of 95 % of RRI assay is reported in patients with sustained and not intermittent ureteral obstruction, and not on acute treatment with vasodilating drugs (non-steroidal anti-inflammatory drugs) [41].

In pregnant women with suspected hydroureteronephrosis, RRI values >0.70 ± 0.04 have a positive predictive value of 85.7 % and a negative predictive value of 91.9 % [44]. In a retrospective study that compared different tools for the diagnosis of renal colic in 300 consecutive patients presenting during pregnancy, the accuracy of ultrasound findings in predicting presence of stones improves from 56 to 72 % when features of obstruction, such as asymmetric absence of ureteral jet, an elevated RRI (>0.7), inter-renal RRI difference >0.08 are included in the ultrasound assessment [45]. Among clinical signs and symptoms, only microscopic haematuria and a history of nephrolithiasis are more prevalent in the stone group. In acute hydronephrosis, high RRI (>0.70) values facilitate diagnosis of obstructive uropathy especially when inter-renal RRI difference >0.08 and absent ureteral jet coexist.

RRI and acute kidney injury

Platt first reported that a marked increase in RRI allows for the diagnosis.

of acute tubular necrosis now called acute kidney injury (AKI), helping physicians to distinguish it from pre-renal failure [17, 46]. An increased RRI (greater than or equal to 0.75) is described in 91 % of patients with AKI, and in 20 % of patients with pre-renal azotemia; the average RRI value is significantly higher in AKI than in pre-renal azotemia (0.85 ± 0.06 vs 0.67 ± 0.09) [46]. Only 11 % of patients with AKI also show renal morphological changes in B-mode. Increased RRI may be associated with various types of pathophysiological changes in the kidney that may occur during AKI: the most important ones are the increase in renal vascular resistance and the injury of the tubulo-interstitial compartment (Fig. 5). In patients with AKI, the increase of RRI occurs very early, and precedes that of creatinine: RRI reaches its maximum value within the first 12 h (creatinine peak after 24 h). When AKI resolves, RRI returns to baseline values following about 1 week after the onset of AKI, whereas creatinine normalization takes about 2 weeks [47]. In a study on critically ill patients, the increase in RRI values anticipates cystatin C as a predictor of AKI onset, and better predicts renal failure progression to dialysis [48]. When RRI values are monitored on septic patients with marked systemic hypotension (<65 mmHg), the increase in the average systolic pressure from 65 to 75 mmHg by catecholamine administration is associated with a contemporaneous decrease in RRI. In these patients, an RRI decrease documents that amines can restore renal perfusion [49].

Recently, RRI is reported to predict the occurrence of AKI in selected populations of patients with septic shock, and during the post-operative period after cardiac surgery [50, 51]. A high RRI is an independent predictor of renal failure in patients undergoing surgery, and can highlight occult bleeding in patients with polytrauma. Darmon et al. suggest that a decrease in RRI may anticipate renal functional recovery after AKI in critical patients who needed mechanical ventilation [52]. High (>0.75–0.80) RRI values predict the occurrence of AKI in patients at high risk, allow for early detection of AKI occurrence, monitor AKI severity, and are associated with worse renal function recovery in AKI patients.

RRI and arterial renal stenosis—the hemodynamic impact and the ischemic kidney

The Doppler parameters used to define a stenosis as hemodynamically significant are well standardized, and can be divided into "major or direct", and "minor or indirect", or even "intrarenal" or "extrarenal" parameters. The criteria for severity of renal artery stenosis suggested by Zierler and Strandnes and published in the *American Journal of Hypertension* 1996, are still in use [53]. Currently, RRI assay is the only Doppler parameter that provides information about the total vascular impedance of the parenchymal circle.

A >75–80 % renal artery stenosis is associated with very low (<0.60) RRI values and with inter-renal RRI differences >0.12. These ultrasound findings suggest that the ischemic kidney is protected by a marked vasodilatation, modulated by the self-regulating intrarenal mechanisms, and predict a good outcome of revascularization in terms of blood pressure control and renal function recovery [54]. The coexistence of chronic renal disease that independently increases the RRI can hide the hemodynamic effect of renal artery stenosis, and limit the information obtainable with Doppler ultrasound. Recently, an RRI >0.73 measured in the kidney contralateral to renal artery stenosis is the strongest predictor of renal function worsening after renal revascularization also adjusted for male gender, regional angioplasty without stenting, obesity, pulse pressure >75 mmHg and serum creatinine >1.8 mg/dl [55].

When hypoperfusion due to renal arterial stenosis persists for a long time and becomes chronic, damage of renal parenchyma develops with a progressive reduction of renal

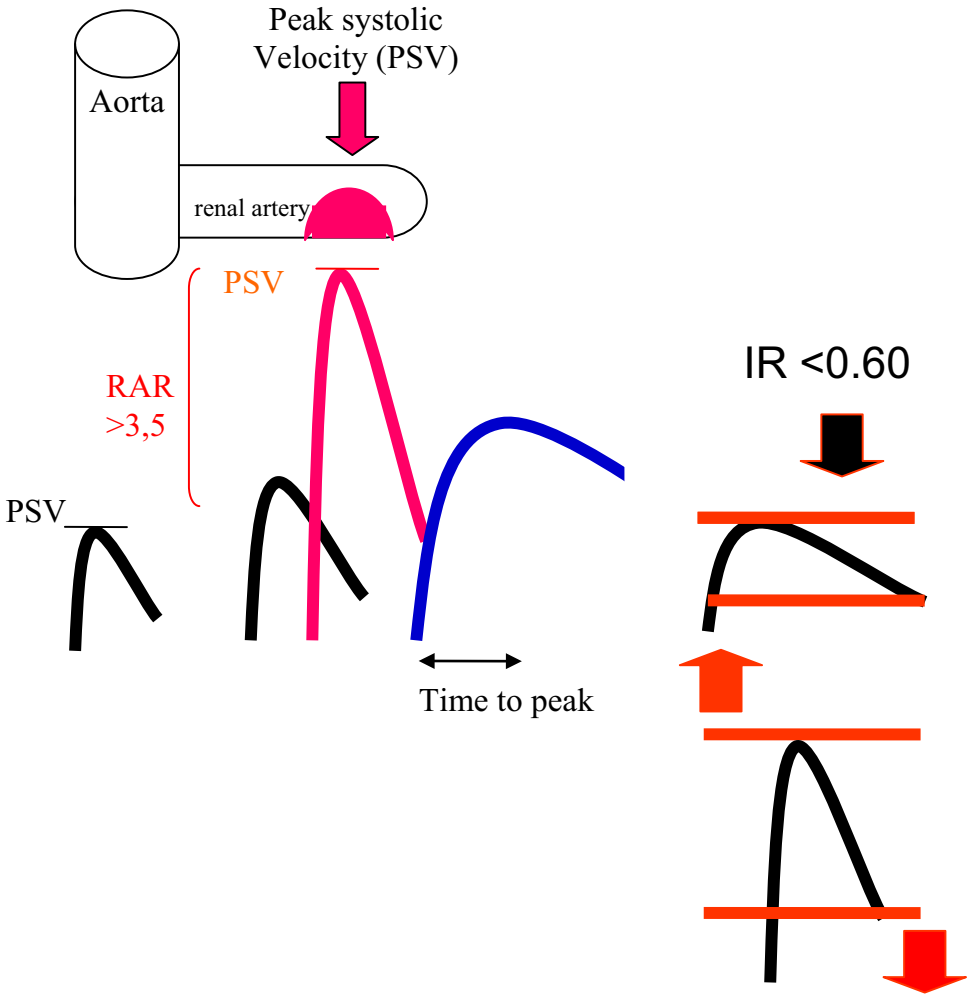

Fig. 5 Schematic representation of Doppler flow patterns assayed at and distal to a hemodynamically arterial renal stenosis; when vascular or parenchymal nephropathies coexist, RRI values increase and the hemodynamic effect of renal artery stenosis is hidden

volume, and increase in interstitial and vascular resistances that result in high RRI [22]. High RRI (>0.75–0.80), especially when associated with renal an interpolar diameter <9 cm and low renal volume, predicts a bad outcome of revascularization [22, 36]. An increased RRI value >0.80 is a strong predictor of renal functional decline in patients with renal artery stenosis, despite correction of the stenosis.

(1) Asymmetric low RRI distal to renal artery stenosis is a good marker of the hemodynamic impact on renal parenchyma. (2)When parenchymal disease coexists and causes a symmetrical increase in RRI values, no information can be obtained on the hemodynamic impact of arterial stenosis. (3) High asymmetric RRI values (0.80) distal to stenosis with low interpolar diameter and volume of the ischemic kidney are associated with a bad outcome after revascularization. (4) High symmetric RRI values are the mirror of systemic rather than renal parameters, and in these patients, the predictive role of RRI for revascularization outcome is under debate.

The doubts-is RRI a marker of systemic atherosclerotic burden or of renal damage?

RRI and subclinical renal organ damage in hypertension

In hypertensive subjects, the renal Doppler flow RRI is validated as a noninvasive measure of renal hemodynamics, as a clinical marker of target organ damage, and as a prognostic predictor of renal and CV outcomes [10].

To define subclinical renal damage, albuminuria is measured, and the combination of eGFR and albuminuria is a useful predictor of CV disease. RRI evaluation is also suggested for the detection of preclinical renal damage and in untreated patients with primary hypertension and normal renal function, a high RRI (>0.70) highlights subclinical signs of renal organ damage; specifically, RRI shows a direct relationship with the amount of urine albumin excretion [56]. During the progression of hypertensive renal damage, high RRI values are often associated with

mild reduction in glomerular filtration rate and increased albuminuria or both [56]. In hypertensive patients, high >0.70 RRI is a marker of renal dysfunction evaluated at 12 months by Cystatin C determination [57]. Moreover, RRI is an independent predictor of worse CV outcomes in 426 patients with primary hypertension and no previous CV disease followed for a mean of 3.1 years [58]. An evaluation of both eGFR and RRI instead of albuminuria might be another investigative option to identify essential hypertensive subjects without clinical evidence of renal damage and cardiovascular disease, predisposed to worse outcomes.

In chronic hypertensive patients undergoing antihypertensive therapy with no microalbuminuria and normal renal function, higher RRI values are found in those subjects with hyperuricemia, or low grade inflammation (PCR > 2 mg/dl, both of which are associated with tubulo-interstitial inflammation and endothelial dysfunction [25, 26]). Moreover, experimental data show that hyperuricemia causes glomerular hypertension, vasoconstriction and ischemia, and is a potent stimulus for tubulo-interstitial inflammation and fibrosis [59].

Dynamic evaluation of RRI in normoalbuminuric patients with newly diagnosed hypertension shows that a decrease in RRI induced by nitroglycerine is lower in hypertensives than in controls despite similar baseline RRI [60]. Reduced renal vasodilatation is independently related to arterial stiffness, and suggests a major role of hemodynamic load in determining early renal microvascular alteration in hypertension. As a whole these findings strengthen the possible role of RRI determination in understanding the intricate link between hypertension and renal target organ damage, until now mainly supported by the relationship between hypertension and microalbuminuria. The unifying mechanism that accounts for the different roles of RRI as a marker of target renal damage and prognostic predictor of renal and cardiovascular outcomes is suggested by recording aortic pressures, aortic and peripheral pulse wave velocities and RRI in 133 hypertensive patients: [1] RRI depends strongly on the aortic pulse pressure and aortic stiffness; [2] it correlates inversely with the femoral reverse-flow and diastolic forward-flow indices; and [3] it predicts urinary albumin excretion together with the aortic pulse pressure [10]. In hypertensives, the altered renal hemodynamics resulting from increased central pulse pressure and aortic stiffness contribute to the development of renal microvascular renal damage. Every 0.1 increase in renal RRI is associated with a 5.4 fold increase in the adjusted relative risk of albuminuria [10]. Increased systemic arterial stiffness underlies the strict relationship between RRI and atherosclerotic damage such as left ventricular hypertrophy, carotid intima media thickness and ankle brachial index [61, 62]. Atherosclerosis increases arterial stiffness, predisposes the renal circulation to a greater hemodynamic load (pulse pressure) and to higher renal microvascular resistance. On the other hand, high RRI may contribute to systemic arterial stiffening by renal dysfunction and activate a self-perpetuating process.

Scarce data are available in literature about the effect of pharmacological therapy on RRI values; whether and how the decrease in RRI values could result in an improvement in renal damage and in renal and CV outcomes is unknown. This limitation plays a major role in the underuse of RRI in clinical practice because the advantages are not clear and doubtful. In hypertensive patients, RRI is a clinical marker of target organ damage, signals systemic atherosclerotic burden, and is a prognostic predictor of renal and cardiovascular outcomes. Clinical relevance is yet to be investigated.

RRI and renal damage in diabetes

RRI is able to detect early renal damage in type 1 and 2 diabetic patients: when renal function is normal and albuminuria is absent, increased RRI predicts the occurrence of albuminuria [63]. Most importantly in patients without microalbuminuria, RRI values >0.70 independently predicted the occurrence of diabetic nephropathy [60]. In type 2 diabetic patients of new diagnosis, RRI values are higher than those of newly diagnosed hypertensive subjects, and the vasodilatation induced by nitroglycerine is significantly lower [60]. Pulse pressure is a strong predictor of impaired RRI decrease in hypertensive patients and diabetics, but in the latter, impaired vasodilatation is significantly related to glycated hemoglobin and systolic pressure. In patients with diabetic nephropathy, the post-glomerular vessels are the major contributors to increased resistance, whereas the pathognomonic histological sign of hypertensive nephropathy is pre-glomerular arteriolar hyalinosis disease.

These findings suggest that in diabetic patients, renal vasculature may be compromised even in the presence of early glucose metabolism impairment, as in prediabetic condition where systemic vascular dysfunction and increased arterial stiffness are already present [60].

Accordingly in hypertensive patients with no albuminuria and normal renal function, the coexistence of diabetes is associated with higher RRI values despite similar PWV in hypertensive patients with and without diabetes [64]. In diabetic subjects with albuminuria and reduced creatinine clearance, RRI >0.80 predicts a worse renal outcome [65]. RRI is an early marker of diabetic nephropathy, and can anticipate microalbuminuria. High RRI (>0.80), select diabetic patients with worse renal outcomes.

RRI and renal damage in chronic kidney disease

The pro of studying patients with chronic kidney disease of any causes is that an increased RRI >0.80 correlates with the rate of decline in renal function, and predicts the course of the disease during 3-years follow-up (Fig. 6) [66]. Proteinuria (>1 g/day) and creatinine clearance (<40 ml/min) are also important indicators of disease progression. However, in terms of positive and negative prediction, RRI demonstrates superior utility. High RRI values are not secondary to differences in pulse rate or in the use of antihypertensive medications [66]. Sugiura and Wada show that high (>0.70) RRI as well as proteinuria and low eGFR and hypertension are independent risk factors for the progression of CKD (4-year follow-up), indicating that RRI can be used as an additional tool for predicting the progression of CKD [67]. The initial measurements of RRI in patients with various nephropathies at the time of renal biopsy is associated with severe interstitial fibrosis and arteriolosclerosis and glomerular filtration rate at 18 months. High RRI may identify patients at high risk of end stage renal disease [68]. In the high RRI group >0.70 of 202 patients with chronic kidney disease who underwent renal biopsies, RRI ≥0.7, hypertension, proteinuria, and low eGFR at diagnosis are independent risk factors for worsening renal dysfunction. In conclusion, RRI in CKD patients is considered a marker of renal function, histological damage, and renal prognosis, and a possible determinant of the response to steroid therapy (0.68). In middle age and elderly hypertensive subjects, the relationship between high RRI and cardiovascular and renal outcomes is confirmed, and the combination of (< 40 ml/min) eGFR and high RRI values is a powerful independent predictor of worse outcome even when adjusted for traditional cardiovascular risk factors [58]. The independent role of RRI in outcomes is also maintained for subjects with an eGRF <60 ml/min.

It is noteworthy that patients with both decreased eGFR and increased RRI have a significant burden of CV risk factors and a higher risk of the primary composite end points as compared with those with either isolated decreased eGFR or increased RRI. Although both eGFR and increased RRI reflect renal dysfunction, the pathophysiological mechanisms leading to these abnormalities may be, at least in part, different. It has been shown that a decrease in eGFR is associated with oxidative stress, subclinical inflammation, increased homocysteine, insulinemia, and coagulability. Increased RRI might be considered a marker of systemic atherosclerotic vessel damage, and compounded with reduced eGFR it may significantly increase the cardiovascular and renal risk [61] (Fig. 7). Data obtained in renal transplanted recipients strongly

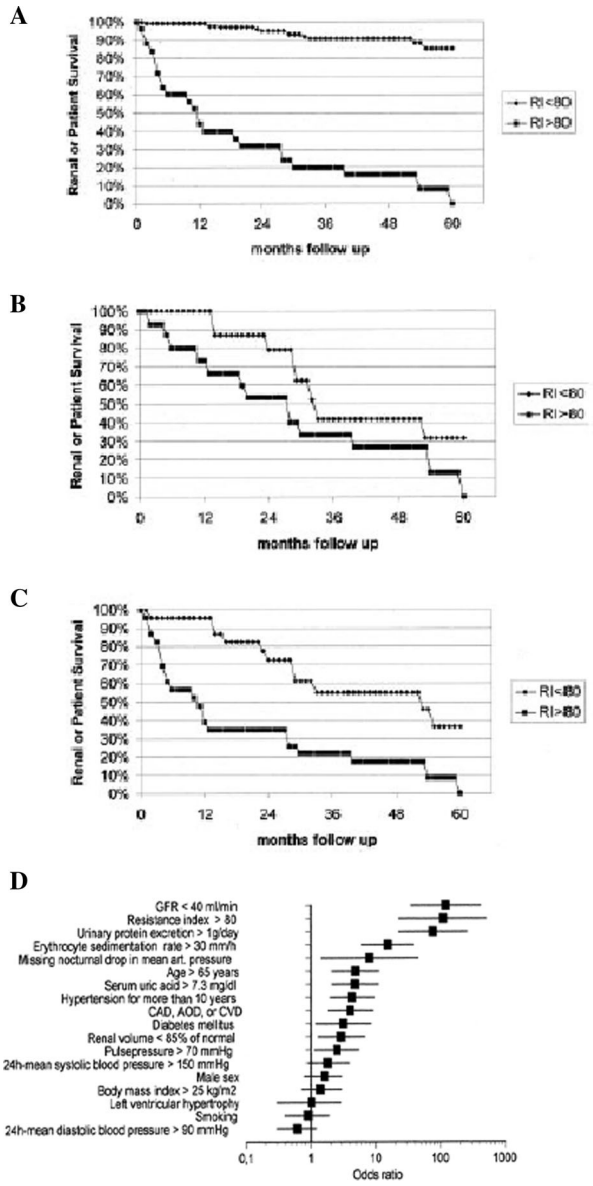

Fig. 6 RRI is an independent predictor of renal or patient survival in 162 patients newly diagnosed with renal disease divided according to resistance index values > or <0.80 [66]. **a** Kaplan–Meier analysis of the length of time to a >50 % reduction of creatinine clearance, dialysis dependence, or death, calculated separately for the 137 patients with RRI values <80 and for the 25 patients with RRI ≥80. **b** Creatinine clearance matched pair analysis. Kaplan–Meier analysis of the length of time to a >50 % reduction of creatinine clearance, dialysis dependence or death, calculated separately for 23 pairs of patients matched for creatinine clearance (RI < 0.80:32 + 13 ml/min/kg BW; RI > 0.80:32 + 17 ml/min/kg/BW. **c** Protenuria matched pair analysis. Kaplan–Meier analysis of the length of time to a >50 % reduction of creatinine clearance, dialysis dependence or death, calculated separated for 15 pairs of patients matched for protenuria (RI < 0.80:2.3 +1.6 g/day; RI > 0.80: 2.3 + 1.7 g/day). **d** Univariate odds ratios for worsening renal function or death, with 95 % confidence intervals, associated with various baseline parameters. Only impaired creatinine clearance and elevated creatinine concentrations have a predictive value as strong as the resistive index value. Reproduced from Radermacher et al. [66]

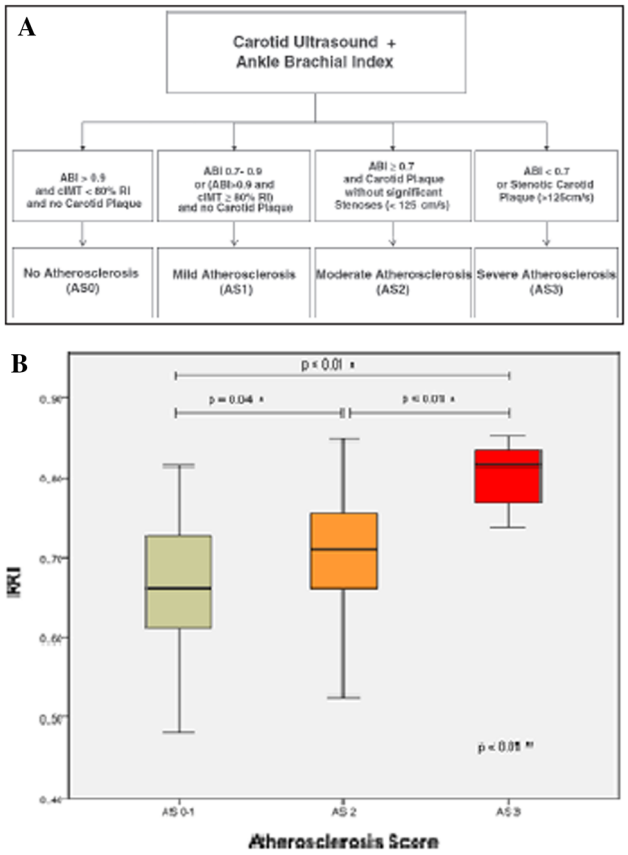

Fig. 7 **a** Definition of the atherosclerotic score that was determined by the values obtained by ankle brachial index (ABI) and carotid ultrasonography. cIMT, carotid intima-media thickness. **b** RRI changes according to the increase in the atheromatosis score [61]. The relationship between RRI and atherosclerotic burden was investigated in 202 patients (36.7 % women) with essential hypertension. Reproduced from Calabia et al. [61]

support that the predictive role of RRI for renal and CV outcome is expressive of systemic and not renal determinants [7].

Conclusions

The use of RRI in clinical practice is limited by the incomplete knowledge regarding all renal and extra-renal patho-physiological determinants that can combine to modulate RRI values differently in different subjects. In acute conditions such as hydronephrosis and AKI, renal determinants play a major role, and RRI can directly monitor renal damage. In vascular and parenchymal nephropathies, the role of renal and extrarenal determinants must be analyzed individually according to subjects' clinical characteristics and the value of the RRI by the internist searching for a marker of target organ damage in hypertension or diabetes, or for an independent predictor of renal and CV outcome. We agree with Radermacher who wrote: "an increase in the resistive index to more than 0.80 may be observed in very old recipients (>85 years of age) with low elasticity and a high risk of death, but may also be seen in a young patient with reduced renal blood flow and preserved elasticity, and confers a high risk of renal failure in this context" [69].

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Compliance with ethical standards

Conflict of interest None.

Statement of human and animal rights This article does not contain any studies with human participants or animal performed by any of the authors.

Informed consent No informed consent is required.

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