Renal ultrasound (and Doppler sonography) in Hypertension:an update

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Abstract

Ultrasound (US) allows the non-invasive evaluation of morphological changes of kidney structure (by means of B-Mode) and patterns of renal and extrarenal vascularization (by means of color-Doppler and contrast-enhanced US). In hypertensive subjects it offers a relevant contribution to the diagnosis of early renal damage, acute or chronic nephropathies and nephrovascular disease. However, morphological changes are often detected late and non-specific and in recent years evidence has increased regarding the clinical relevance of renal resistive index (RRI) for the study of vascular and renal parenchymal renal abnormalities. RRI is measured by Doppler sonography in an intrarenal artery, as the difference between the peak systolic and end-diastolic blood velocities divided by the peak systolic velocity. At first RRI was proved to be a marker of renal disease onset and progression; later the influence of systemic vascular properties on RRI was shown and authors claimed its use as an independent predictor of cardiovascular risk rather than of renal damage. Indeed, renal vascular resistance is only one of several renal (vascular compliance, interstitial and venous pressure), and extrarenal (heart rate, pulse pressure) determinants that concur to determine RRI individual values but not the most important one. The clinical relevance of RRI measurement as a surrogate endpoint of specific renal damage or/and as surrogate endpoint of atherosclerotic diffuse vascular damage is still debated.To summarize, from the literature: a) In hypertensives with normal renal function and no albuminuria,especially in younger people, RRI is an early marker of renal damage that is especially useful when hypertension and diabetes concur in the same subjects. In these subjects RRI could improve current clinical scores used to stratify early renal damage. In older subjects RRI increases in accordance with the increase in systemic vascular stiffness and, because of this close relationship, RRI is also a marker of systemic atherosclerotic burden and the role of renal determinants can weaken. The clinical relevance was not specifically investigated. b) In transplant kidney and in chronic renal disease high (>0.80) RRI values can independently predict renal failure.The recent claim that systemic (pulse pressure) rather than renal hemodynamic determinants sustain this predictive role of RRI, does not significantly reduce this predictive role of RRI. c)

Doppler ultrasound allows diagnosis and grading of renal stenosis in both fibromuscolar dysplastic and atherosclerotic diseases. Moreover, by RRI assay Doppler ultrasound can indirectly measure the hemodynamic impact of renal artery stenosis on the homolateral kidney, by virtue of the stenosis-related decrease in pulse pressure. However, in elderly subjects with atherosclerotic renal artery stenosis coexisting renal diseases can independently increase RRI by the augmentation in renal vascular stiffness and tubulo-interstitial pressure and hidden changes due to renal artery stenosis.

Key words: renal resistive index, ultrasonography, hypertension, renal disease,renal artery stenosis.

Introduction

The pathophysiological relationship between increased blood pressure and kidneys is complex. High blood pressure causes progressive renal damage but also vascular or parenchymal renal disease can sustain increase in blood pressure.
Ultrasound (US) has a key role in evaluating both morphological changes of kidney structure (by means of B-Mode) and patterns of renal and extrarenal vascularization (by means of color-Doppler and contrast-enhanced US), thus contributing to the diagnosis of early renal damage, acute or chronic nephropathies and nephrovascular disease in hypertensive patients. Maximum renal diameter is a morphological marker of CKD. It decreases contemporarily to Glomerular Filtration Rate (GFR) and a significant correlation of both renal diameter and cortical thickness with renal function has been demonstrated (1). A direct correlation between the number of functional renal units, nephrons, renal mass, renal function and ultrasound-measured renal volume has also been reported. Kidney size was measured by US which compared with other radiologic methods gave results that came closest to the actual size of the kidney measured during surgery (2). Ultrasound-measured volume of kidneys correlates well with the stage and the progression of CKD and can be used to evaluate CKD progression. However, ultrasound-detected morphological changes are late and not specific. In recent years increasing attention has been paid to the study of renal resistive index (RRI) obtained by Doppler arterial waveform analysis of intrarenal arteries as an independent marker of early renal damage when albuminuria and glomerular filtration rate are still normal, and as an independent predictor of renal failure progression in chronic renal disease (3-6).
Infact, as well synthesized in the review by Viazzi et al (7), not only does Doppler ultrasonography detect renal macroscopic vascular abnormalities that allows diagnosis and grading of renal artery stenosis, but it also identifies changes in blood flow at the microvascular level that reflect functional or structural changes within the kidneys. Specifically, acute functional changes in renovascular resistance physiologically induced by sympathetic activation or pharmacologically by ACE inhibitors (8, 9) ,acute increase in tubulo-interstitial pressure by hydronephrosis or acute kidney injury and chronic structural damage of arteriolar or tubule-interstitial rather than glomerular compartment do affect RRI.

Recent clinical and experimental evidence indicates that increased RRI in patients with primary hypertension with normal or reduced renal function may reflect and score changes in intrarenal perfusion because of arteriolar and/or tubule-interstitial renal damage that can occur independently of glomerular damage. Moreover,in hypertensive patients high RRI is also associated with worse systemic hemodynamics and atherosclerotic burden. Due to this relationship ,RRI has been also proposed as a new independent marker and predictor of systemic cardiovascular risk in asymptomatic subjects. The clinical relevance and the possible therapeutic implications of this use need dedicated studies [10,11]. This review tries to give information on the knowledge of physiopathological renal and extra-renal determinants of RRI, necessary for the correct use of RRI ultrasound measurement in clinical practice when focused on the study of early and late renal damage in essential hypertension and in the diagnosis and grading of renal artery stenosis. Specifically, we want to show whether and when the measurement of RRI should be considered as a specific marker of renal damage to use together and in addition to Glomerular Filtration Rate (GFR) and microalbuminuria or as a parameter of systemic cardiovascular risk to use together and in addition to intima-media-thickness and other surrogate ultrasound endpoints for cardiovascular risk stratification of asymptomatic patients.

According to recent recommendations by the major societies for the study of hypertension (the American Heart Association, the American College of Cardiology and the Centers for Disease Control and Prevention, the American Society of Hypertension and the International Society of Hypertension, the Canadian Hypertension Educational Program, the European Society of Cardiology and the European Society of Hypertension, the National Institute for Health and Care Excellence, The French Society of Hypertension, the Taiwan and the Chinese Society of Hypertension) (12-20), the study of hypertensive patients by renal ultrasonography is mainly dedicated to patients with the clinical suspicion of secondary hypertension. This is because ultrasound can detect the presence of renal parenchymal disease, polycystic renal disease, and urinary tract obstruction. Specifically, when clinical characteristics point to renovascular hypertension, ultrasound screening is recommended to confirm or rule out the diagnosis of renal artery stenosis, grading the stenosis and investigating its hemodynamic impact on the homolateral kidney. At present, the ultrasound study of renal target-organ damage in essential hypertension has not been codified; and the determination of GFR and of albuminuria excretion rate are recommended.

This review wants to give strong support to the use of RRI for investigating early and late renal damage in hypertensive patients, as an independent predictor of renal failure and/or of cardiovascular risk.To have a high RRI selects subjects at increased risk of developing renal failure and of having cardiovascular events beyond the pattern of other current renal and ultrasound markers of risk.

Renal Resistive Index (RRI)

RRI, derived from the Doppler spectrum of intrarenal (segmental or interlobar) arteries, is obtained by the difference between maximum (peak systolic) and minimum (end-diastolic) flow velocity to maximum flow velocity (Figure 1):

$$RRI = \frac{\text{(peak systolic velocity (PSV) –end-diastolic velocity (EDS))}}{\text{Peak systolic velocity (PSV)}}$$

The morphology of Doppler spectrum of RRI is mainly determined by the velocity/time (V/t) curve that is assayed along the main renal artery, that can be defined as a “low resistance” curve. The systolic phase quickly increases to peak velocity and is followed by a progressive and gradual deceleration phase with a telediastolic velocity that does not decrease below 30-40 cm/sec. This Doppler spectrum is common and peculiar to all parenchymal flows, because a sufficient oxygen supply must be assured throughout the cardiac cycle (21).

RRI was introduced in 1950 and initially proposed for the semi-quantitative assay of intra-renal vascular resistance by Pourcelot in 1974 [22]. He showed that the ratio was influenced by changes in vascular resistance distally to the point of RRI assay. The term RRI has been kept to the present time, even if the strict relationship between RRI and actual renal vascular resistance has become very weak (10,11).

According to these findings RRI was initially used for the diagnosis and follow-up of acute and chronic renal disease [3,7] which are associated to dynamic and/or structural changes in intra-renal vessels. Later on RRI was proved to be a strong independent predictor of renal failure [3,5]. However, in the meantime growing evidence showed that RRI is the result of many intra and extra-renal determinants and that renal vascular resistance is only one of these, and not the most important (23)(Figure 2). Remarkably, in 1991 Gosling et al [24], and in 1999 Bude and Rubin [25], clearly showed by in vitro experiments performed in simple artificial circuits, that RRI is dependent on both renal vascular compliance and resistance, becoming less dependent on resistance as compliance decreases. When

compliance is zero, RRI is independent of changes in renal vascular resistance. Moreover, new experimental [10,26] and clinical data (10,11) were obtained showing that RRI was markedly affected by the changes in renal (renal interstitial and venous pressure) and systemic (pulse pressure) determinants of vascular compliance, and only scarcely by the chronic increase in renal vascular resistance. In chronic renal diseases and in transplant recipients, RRI mainly depends on systemic vascular compliance assayed as pulse pressure, rather than renal vascular properties [10,11]. In these patients the increase in RRI is strictly associated with the decrease in systemic vascular compliance assayed as pulse pressure that is negatively modulated by aging and traditional cardiovascular (CV) risk factors, among which hypertension plays a major role (10). According to this point of view, in hypertensive patients with and without renal function impairment, the increase in RRI predicts worse renal and general outcomes, as a marker of systemic atherosclerotic burden rather than of local renal damage. However, this statement is still a matter of debate and do not weaken the clinical relevance of RRI measurement for risk scoring. On the contrary full agreement was reached on the clinical use of RRI as a specific marker of renal damage, in subjects affected by those renal pathologies that can promote the progression of renal damage in hypertensive patients, i.e. hydronephrosis, renal vein thrombosis, increased abdominal pressure and acute kidney injury. In all these conditions the acute and marked increase in renal tubule-interstitial and venous pressure due to hydrostatic or inflammatory edema leads to the direct increase in RRI values (23).

RRI threshold in clinical practice

Aging is associated with a progressive quantitative decrease of renal microvascular bed and with an increased thickness of tunica media of renal arterioles (Figure 2). This determines a decrease in the lumen/vessel wall ratio. Both these changes result in a progressive increase in RRI (27) that can be amplified by the contemporaneous increase in systemic arterial stiffness. The steep age-dependent rise in RRI values is specific to the renal vasculature and is not seen in other vascular beds. The age-related hypertrophic remodelling of the vessel wall of renal microvessels can be further amplified by hypertension and/or diabetes (28,29) . In healthy adults most authors use >0.70 as the cut-off limit for pathological RRI and do not establish normal values according to age. However, in healthy subjects >70 yrs, RRI >0.70 can be measured in the absence of renal diseases, whereas in subjects aged >40 yrs can be the first marker of renal damage that anticipates GRF reduction and the occurrence of albuminuria (27). Further an

emerging clinical issue is the evaluation of the actual renal function in elderly normal patients or diabetics, since the estimated values of GFR by math formula suffer of limits in these subgroups. So that, in elderly subjects with normal renal function or diabetics, RRI assessment might be considered an other non-invasive way to reveal early renal damage.
In a recent large multicentric family-based population study, age was confirmed as a determinant of RRI. Ponte et al (30) also showed that the relationship of RRI with age is nonlinear and that RRI increases sharply after the age of 40.
In the same multicentric study female sex was associated with higher RRI values due to hormone differences and the fact that RRI has a genetic tract was reported (30); the clinical relevance of these findings must be investigated by dedicated studies.
In newborns and in children under the age of four, RRI >0.70 can be found because of renal anatomical structure in this period and is not associated with renal pathologies (31).

Systemic and renal determinants of RRI

In any arterial vascular tract, Doppler waveform is the integrated result of what happens before and downstream from the point where the flow is assayed.

a) Systemic and extrarenal determinants

Stiffness-related Systemic pulse pressure

The ratio of systolic to diastolic blood pressure (see RRI equation) is an inverse function of pulse pressure. Thus, for any given intra-renal vascular resistance an increase in systemic systolic arterial pressure promotes a higher peak renal velocity and/or a decrease in diastolic arterial pressure. That results in a lower end-diastolic velocity . As a direct consequence, in vivo any increase in systemic arterial stiffness that causes increased pulse pressure is associated with high RRI values, both in physiological (aging) and pathological (hypertension) conditions (Figure 2c). Changes in pulse pressure can also be tonic or phasic, as during an infusion of L-NG-monomethyl argirine (L-NMMA), an inhibitor of endothelial NOS. Neither RRI under baseline conditions nor RRI during L-NMMA infusion were related with renal vascular resistance or renal perfusion, assayed by para-aminohippuric acid and insulin clearance [32]. On the contrary, RRI changed according to variations of central pulse pressure.
The relationship between RRI and pulse pressure has also been investigated in recipients of kidney transplants where systemic pulse pressure is recipient-specific, whereas the compliance of interlobular arteries is donor specific; in these kidneys RRI correlated with the age of the recipient but not of the donor, with recipient pulse pressure but not parameters of allograft function and with RRI of other (i.e. splenic) districts of the recipient

(33). As a whole the findings observed in transplant recipients strongly support that RRI primarily reflects the properties of the systemic vasculature that can hidden or weaken the effects of local renal damage on intrarenal vasculature.

Stenosis-related pulse pressure

Severe (>80%) renal artery thoracic or sovra-renal abdominal aorta or valvular aortic stenosis all decrease pulse pressure in vascular districts distal to stenosis, and decrease RRI values (<0.60) as a result of low peak systolic velocity (Figure 2,2a). The dampened flow is revealed by the peculiar Doppler wave pattern characterized by a “tardus”, slow, and “parvus”, small pulsus (Figure 2 and 3). The finding of low RRI in the homolateral kidney and the lateralization of RRI (delta >0.05) is indirect but reliable proof of severe renal artery stenosis (Figure 4). In fact the gradual reduction of renal perfusion pressure up to 40% does not substantially change renal blood flow and glomerular filtration rate, thanks to the self-regulating mechanisms of intrarenal circulation. In these conditions RRI is not affected. This mechanism becomes ineffective when morphological renal arterial stenosis is >75%, renal perfusion pressure falls >40% and renal systolic pressure is <70-80 mmHg [34,35]. This renal stenosis is defined hemodynamically significant, because it activates the renal renin angiotensin system [21,36] and demodulates Doppler waveform at intrarenal arteries. However, when distal renal vascular disease coexists due to chronic ischemic kidney, the hemodynamic effects of renal artery stenosis may be hidden. In these patients RRI is symmetrically high, not lateralized and the hemodynamic effect of arterial stenosis on renal parenchyma cannot be evaluated by Doppler ultrasound (21,23)(Figure 4) (see also *Ultrasound diagnostics of renal artery stenosis,page 14).*

Heart rate

Changes in heart rate can affect RRI independently from the other hemodynamic parameters because of changes in diastolic duration that modulate end-diastolic velocity. During bradicardia diastolic duration increases and high RRI is measured. On the contrary during tachicardia diastolic duration shortens and RRI decreases (Figure 2,2a and 2c).

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 ex vivo rabbit kidney model elevations in ureteral pressure were significantly correlated with increased RRI values, mean renal vascular resistance (pressure/flow) and decreased mean conductance (flow/pressure) [37]. 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(Figure 2,1c). Also renal hematoma can acutely increase the pressure of interstitial compartment and elevate RRI (38).

Most importantly, acute kidney injury (AKI) is associated with an acute increase in interstitial pressure because of sustained vasoconstriction and ischemic and inflammatory damage of the tubulo-interstial compartment by sustained hypoperfusion. In all these clinical conditions the occurrence, severity and progression of renal damage can be well monitored by changes in RRI values (38-41). Recently, in critical patients admitted for medical, surgical or trauma disease, high RRI values at admission were significantly and independently associated with in-ICU mortality and persistent AKI at ICU discharge (43).

Histological renal parameters - RRI and the tubulo-interstitial compartment

Twenty years ago Platt et al showed that RRI was significantly higher in nephropathies with tubulo-interstitial and/or vascular injury than in isolated glomerulopathies [44].Glomerular arterial resistance, that accounts for about 20% of total renal vascular resistance, scarcely concurs to the determination of RRI; and nephropathies characterized by prevalent glomerular involvement are not associated with increased RRI. RRI is not a marker of renal function (Figure 2).

The studies on the relationship between tubular, interstitial and arterial damage and RRI in renal disease and in kidney transplants show conflicting results: according to Ikee et al, only arteriolosclerosis out of all histological parameters independently correlated with RRI in chronic renal disease [4], whereas in renal transplants investigated at 3,12 and 24 months after transplantation RRI was not associated with any renal allograft histological features. On the contrary, other Authors reported that high RRI values were related to more severe tubulo-interstitial damage score, and an association between RRI values and the extension of interstitial fibrosis was shown, probably due to the rise in pressure exerted by interstitial fibrosis on adjacent vessels. Remarkably, interstitial fibrosis closely correlated to renal function and long-term prognosis and could underline the role of RRI as an independent marker of renal and clinical outcome in patients with CKD [5,6].

The possible use of RRI as a marker of tubulo-interstitial nephropathy is supported by the findings that the detection of high RRI values allowed 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 was still preserved [45]. Moveover, in hypertensive patients with normal creatinine clearance and no albuminuria, high RRI values were associated with low grade inflammation (Protein C reactive >2 mg/dl) and hyperuricemia (>6.5 mg/dl) [46-47]. Both sustain a tubulo-interstitial nephropathy. In hypertensive patients, serum uric acid strongly correlated with RRI, independently of renal function or albuminuria, but the altered intrarenal hemodynamics did not explain the pathophysiology of hyperuricemic renal damage (48).

A generalized consensus was reached that tubulo-interstitial and not glomerular nephropathies affect RRI and that RRI does not measure renal function.

Role of arterial vascular resistance

Based on early experimental animal data [25,37], RRI was long considered to directly mirror intrarenal resistance, thus allowing a non-invasive glimpse into intrarenal (patho)physiology [49]. Under physiological conditions RRI assay could detect phasic increase in renal vascular resistance induced by sympathetic activation obtained by cold pressor test or handgrip; in the same subjects the increase of blood volume by acute hydration resulted in an RRI decrease [27]. Repeated daily sessions of music-guided slow-breathing increased parasympathetic modulation and decreased RRI early in the study .These changes were being followed by a positive modulation of baroflex sensitivity and decrease in blood pressure [50]. In patients with heart failure high RRI values were associated with increased intrarenal vascular resistance due to neurohormonal hyperactivity and independently predicted heart failure progression [51]. In septic shock Doppler ultrasonography and RRI measurements may help determine in each patient the optimal mean aortic pressure for renal blood flow and may be a relevant end-point to titrate the haemodynamic treatment by fluid and norepinephrine administration (52).Catheter-based renal sympathetic denervation in patients with resistant hypertension reduced RRI probably through a decrease in intraparenchymal resistance, not mediated by reduction in systolic blood pressure [53]. As a whole these findings sustain that the RRI can detect phasic changes in renal vascular resistance.

On the contrary, RRI changes during dynamic vasodilation caused by nytroglicerin or (L-NMMA) infusion were poorly associated with the concurring direct measurement of renal resistance by scintigraphy, even if the changes in RRI and in renal vascular resistance moved in the same direction. Rather, RRI changes were directly related to changes in pulse pressure (32). Increased RRI has been shown to correlate with systemic arterial

stiffness measured by ambulatory blood pressure derived by Ambulatory Arterial Stiffness Index (54). Moreover, a close relationship between RRI and other markers of systemic atherosclerotic burden, as intima-media thickness and ankle brachial index, was shown in hypertensive patients with chronic renal disease, independently of renal damage (55).
For many years the role of high RRI values as an independent marker of renal outcome in patients with CKD was mainly due to the assumption that RRI increase was determined above all by the progressive "tonic" increase in vascular resistance because of: a) decrease in arterial compliance due to renal arteriosclerosis; b) elevation of extra-vascular renal pressure exerted by interstitial fibrosis in adjacent vessels; c) vasoconstriction secondary to hypoxia and to loss of capillaries associated with renal fibrosis. All these are associated with decline in renal function (23).
In recent years evidence has been gathered around RRI being an independent marker of renal and cardiovascular outcomes, because it measures systemic and not renal hemodynamic parameters, and reflects systemic vascular disease (56). We agree with O Neill's title "Renal resistive index. A case of mistaken identity" (11). However, there is no doubt that both phasic (sympathetic activation) and tonic (arteriolosclerotic) changes in renal arterial resistance can modulate RRI.

RRI and subclinical renal damage in hypertension

In clinical practice albuminuria is measured to define subclinical renal damage in hypertensive patients, and the combination of eGFR and albuminuria is a useful predictor of CV disease (7). In recent years RRI was also validated as a clinical marker of subclinical renal damage as well as a prognostic predictor of renal and CV outcomes to use in addition to the above mentioned markers in order to improve their performance.
In untreated patients with primary hypertension and normal renal function, high RRI (>0.70) highlights subclinical signs of renal damage and shows a direct relationship with the amount of urine albumin excretion [58]. Further RRI was proved to be a useful index to predict increase in urinary albumin excretion in patients with essential hypertension (7).
With the progression of hypertensive renal damage, high RRI values are often associated with a mild reduction in glomerular filtration rate and increased albuminuria or both [59]. In hypertensive patients high (>0.70) RRI predicts renal dysfunction evaluated at 12 months by Cystatin C determination [60]. Evaluation of both eGFR and RRI instead of albuminuria could be another investigative option to identify essential hypertensive subjects without

clinical evidence of renal damage and cardiovascular disease, predisposed to worse renal and CV outcomes.

In hypertensive patients undergoing chronic antihypertensive therapy with no microalbuminuria and normal renal function, higher RRI values were found in those with hyperuricemia or low grade inflammation (PCR >2 mg/dl), both associated with tubulo-interstitial inflammation and endothelial dysfunction (46). Remarkably, in experimental studies it was found that hyperuricemia causes glomerular hypertension, vasoconstriction and ischemia, a potent stimulus for tubulo-interstitial inflammation and fibrosis [47,61]. Dynamic evaluation of RRI in normoalbuminuric patients with newly diagnosed hypertension showed that the decrease in RRI induced by nytroglicerine was lower in hypertensives than in controls despite similar baseline RRI [62]. Reduced renal vasodilation was independently related to the increase of systemic arterial stiffness and suggests a role of systemic hemodynamic load in determining early renal microvascular alteration in hypertension. RRI determination could help to understand the intricate link between hypertension and subclinical renal damage, till 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 subclinical renal damage and a prognostic predictor of renal and cardiovascular outcomes was suggested by Hashimoto et al (63) who recorded aortic pressures, aortic and peripheral pulse wave velocities and RRI in 133 hypertensive patients: (a) RRI depends strongly on aortic pulse pressure and aortic stiffness; (b) RRI correlates inversely with the femoral reverse-flow and diastolic forward-flow indices; and (c) RRI predicts urinary albumin excretion together with the aortic pulse pressure. In these hypertensive patients the altered renal hemodynamics due to increased central pulse pressure and aortic stiffness contributed to the development of renal microvascular damage marked by high RRI. Every 0.1 increase in renal RRI was associated with a 5.4-fold increase in the adjusted relative risk of albuminuria [63]. According to these findings atherosclerosis increases systemic arterial stiffness, predisposes renal circulation to a greater hemodynamic load (pulse pressure) and results in higher renal microvascular resistance. Increased systemic arterial stiffness underlines the strict relationship between RRI and atherosclerotic damage such as left ventricular hypertrophy, carotid intima media thickness and ankle brachial index [28, 64,65]. On the other hand high RRI might contribute to systemic arterial stiffening by renal dysfunction and activate a self-perpetuating process. Moreover, RRI proved to be an independent predictor of worse renal and CV outcomes in 426 patients with primary hypertension and

no previous CV disease followed for a mean of 3.1 years [66]. We can conclude that in hypertensive patients with normal renal function RRI is an early clinical marker of subclinical renal damage, that can anticipate the occurrence of microalbuminuria, but also signals systemic atherosclerotic burden. For both reasons high RRI is a good predictor of worse renal and cardiovascular outcomes.

The vast majority of RRI measurements reported in literature are carried out in hypertensives on different pharmacological combinations without a wash-out period; this could result in confounding factors for the study of determinants of RRI .Remarkably, scarce data are available in literature (67,68) about the effect of pharmacological therapy on RRI values; whether and how the decrease in RRI values could result in an improvement of renal damage and in renal and CV outcomes is unknown. This fact is mainly responsible for the limited use of RRI in clinical practice and need dedicated studi.

RRI and renal damage in diabetes

RRI can detect early renal damage in patients with diabetes type 1 and 2: when renal function is normal and albuminuria is absent; increased RRI predicts the occurrence of albuminuria [69]. Most importantly, in patients without microalbuminuria RRI values >0.70 independently predicted the occurrence of diabetic nephropathy. In diabetic subjects with albuminuria and reduced creatinine clearance, RRI >0.80 predicts a worse renal outcome (23).

Newly diagnosed Type 2 diabetic patients show higher baseline RRI and lower vasodilatation induced by nytroglicerin than those observed in newly diagnosed hypertensive subjects [62]. Pulse pressure proved to be a strong predictor of impaired RRI decrease in hypertensives and diabetics, but only in diabetic subjects was impaired vasodilatation significantly related to glycated haemoglobin and systolic pressure. Indeed,in patients with diabetic nephropathy the postglomerular vessels were the major contributor to increased resistance, whereas the pathognomonic histological sign of hypertensive nephropathy is preglomerular arteriolar hyalinosis disease.

These findings suggest that in diabetic patients renal vasculature might be compromised even in the presence of early glucose metabolism impairment, as in pre-diabetic condition where systemic vascular dysfunction and increased arterial stiffness are already present. Accordingly, in hypertensive patients with no albuminuria and normal renal function, the coexistence of diabetes was associated with higher RRI values despite similar PWV in hypertensives with and without diabetes (29).

RRI and renal damage in chronic renal disease

In 2002 Radermacher et al reported that in patients with chronic renal disease of any cause, an increased (>0.80) RRI correlates with the rate of decline in renal function and predicts the course of the disease (3). During a mean 3 years of follow up in these patients proteinuria (>1g/day) and creatinine clearance (<40 ml/min) were also important indicators of disease progression, but in terms of positive and negative prediction RRI demonstrated superior utility. High RRI values were not secondary to differences in pulse rate or in the use of antihypertensive medication [3]. Sugiura and Wada [5] showed that high (>0.70) RRI as well as proteinuria, low GFR and hypertension, are independent risk factors for the progression of CKD (follow-up 4 years) and reinforced the feeling that RRI could be used as an additional tool for predicting the progression of CKD. High RRI could identify patients at high risk of end stage renal disease, because 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 a worse glomerular filtration rate at 18 months [6]. In the high (>0.70) RRI group of 202 patients with CKD who underwent renal biopsies, RI ≥ 0.7, hypertension, proteinuria, and low eGFR at diagnosis were independent risk factors for predicting worse renal dysfunction.

In conclusion, according to the above reported findings RRI in CKD patients can be considered an independent predictor of renal failure, histological damage, and worse renal prognosis, as well as a possible determinant of the response to steroid therapy.

In middle aged and elderly hypertensive subjects Doi et al (66) confirmed the relationship between high RRI and worse cardiovascular and renal outcomes and that the combination of (<40 ml/min) eGFR and RRI was a powerful independent predictor of worse outcome, even when adjusted for traditional cardiovascular risk factors. The independent role of RRI in outcomes was maintained also for subjects with a GRF <60 mL/min. It is noteworthy that patients with both decreased eGFR and increased RRI had a significant burden of CV risk factors and a higher risk of the primary composite end points 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, at least in part, be different. (3,23,66). Increased RI could be considered a marker of systemic atherosclerotic vessel damage, and compounded with reduced eGFR it may significantly increase the cardiovascular and renal risk. Data obtained from renal transplant recipients strongly supported that the

predictive role of RRI for renal and CV outcome was the expression of systemic and not renal determinants (10,11).

Resistant hypertension

We have already mentioned that patients with treatment-resistant hypertension showed high RRI (53). In these patients renal denervation was proposed as an attractive opportunity but so far only invasive procedures have been tested with conflicting results. Recently an approach for delivering externally focused ultrasound specifically targeting the perirenal artery tissues has been proposed. The application of acoustic energy creates a thermal field which is capable of ablating renal nerves around the renal artery, up to 1 cm beyond the lumen. In 69 patients with treatment-resistant hypertension who underwent renal denervation with externally delivered focused ultrasound, a good reduction (24/10 mmHg) after 6 months was observed without major side effects (71).Further studies are needed to confirm these first promising results.

Ultrasound diagnostics of renal artery stenosis

Eligibility for ultrasound screening for renal artery stenosis is based on clinical criteria (1,21,72). Screened subjects are mostly adults (especially elderly subjects) with atherosclerotic vascular disease involving multiple districts and stage 2 and 3 CKD without a documented history of renal disease. During a routine ultrasound examination a small kidney (length <9cm) can suggest ischemic damage due to renal artery stenosis. The Doppler parameters used to define stenosis as hemodinamically significant are well standardized and can be divided into " major or direct " and "minor or indirect " , or even "intrarenal or extrarenal" parameters. The criteria adopted by Zierler and Strandnes, published in the American Journal of Hypertension 1996 [73], are still in use. Currently, RRI assay is the only Doppler parameter that provides information on the total vascular impedance of the parenchymal circle (21,72).

Direct criteria are peak systolic velocity (PSV) and the ratio between PSV at renal stenosis and PSV in the aorta (Figure 4); renal aortic ratio (RAR) a- PSV determines the degree of stenosis according to the continuity equation, because PSV is inversely proportional to the cross-sectional area of stenosis. However, PSV is also influenced by current blood pressure, wall vessel compliance, tortuosity of renal arteries and chronic renal parenchymal damage. Hyper-dynamic circle as observed in young people, hyperthyroidism and anemia, can also affect PSV. b-RAR compares the increased

intrastenotic flow velocity in the renal arteries with the reference value measured in the aorta, and permits the decrease of the influence of the above mentioned systemic factors on PSV, measured at renal artery. Under physiological conditions the PSV along the main renal artery ranges between 60 and 120 cm/sec.

We want to remind readers that since eccentric stenosis results in a lower hemodynamic effect at the same angiographic diameter reduction, compared with concentric stenosis , (50% of diameter reduction in concentric stenosis =75% of area reduction, whereas =50% in eccentric stenosis), PSV can rise twice as high at the same diameter reduction in eccentric stenosis. Compared with gold standard angiography, PSV measured by Color Duplex ultrasound shows sensitivities of 71-98% and specificities of 62-98%. Studies usually set the PSV cut-off value for >60% renal artery stenosis at 180-200 cm/s, but they are determined by each author using receiver operating characteristics (ROC) curves, and different values are reported by different authors. It is to be noticed that selecting higher PSV cut-off values results in lower sensitivity and greater specificity in ROC curves compared with angiography (21,72).

The combined use of PSV with RAR allows the increase in sensitivity and specificity of Doppler renal ultrasound to detect severe renal artery stenosis (72).

End-diastolic peak velocity was reported as stenosis criteria for the grading of carotid stenosis, but is markedly influenced by peripheral resistance which increases early in renal parenchymal damage and its use in the grading of renal artery stenosis is discussed .

We would like to point out that only >70-75% RAS causes a relevant post-stenotic pressure drop, activating the renin angiotension system and requiring treatment. Only in high grade drop in post stenotic pressure can the severity of renal artery stenosis be calculated as validated for iliac arteries (21,72).

Indirect criteria are based on the analysis of post-stenotic Doppler frequency spectra found distally to a >70% renal artery stenosis, that depend also on intrarenal wall vessel and extra-vascular compliance and parenchyma function (Figure 4) 1- RRI assayed in the kidney distally to renal artery stenosis shows a decreased difference between maximum and minimum flow velocity with a tardus-parvus spectrum and is lateralized with a difference in RRI >0.05 between the two kidneys, 2-Delayed acceleration time (AT) i.e. delay in the systolic rise from end diastole up to PSV on RRI spectral analysis. These ultrasound findings suggest that the ischemic kidney is protected by marked vasodilation, modulated by the self-regulating intrarenal mechanisms [21,73] which predict a good

outcome of revascularization in terms of blood pressure control and recovery of renal function.

Renal artery stenosis due to fibromuscular dysplasia., usually discovered in young female, is characterized by specific renal vascular modifications and a normal renal function. For this kind of renal artery stenosis has been clearly shown the utility of doppler findings (PSV, RRI) in evaluating the severity of stenosis and the presence of intrarenal hemodynamic modifications before and after interventional procedures when compared to those obtained from the gold standard such as selective renal arteriography (72,73).

In subjects with atherosclerotic renal artery stenosis, the typical post-stenotic criteria can be well evident in patients aged <60, with normal renal function, but not always in older patients with combined arteriolosclerosis and renal damage.These older subjects show high and symmetric RRI. The concurrence of chronic renal disease independently increasing RRI can hide the hemodynamic effect of renal artery stenosis and limit the information obtainable through Doppler ultrasound. Moreover, when parenchymal renal damage is asymmetrical as in pielonephritis, the bias for RRI measurement as marker of severe renal artery stenosis further increases (23)(Figure 4).

Recently, RRI >0.73 measured in the kidney controlateral to renal artery stenosis was the strongest predictor of renal function, worsening after renal revascularization also adjusted for male sex, regional angioplasty without stenting, obesity, pulse pressure >75mmHg and serum creatinine >1.8 mg/dl [74].

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 volume and increase in interstitial and vascular resistance that results in high RRI [75]. High RRI (> 0.75), especially when associated wih renal interpolar diameter < 9 cm and low renal volume, predicts a bad outcome of revascularization (76). An increased RRI value >80 is a strong predictor of renal functional decline in patients with renal artery stenosis, despite correction of the stenosis. As a whole data available in literature can be summarized as follows:

a) Asymmetric low RRI distal to renal artery stenosis is a good marker of the hemodynamic impact of renal artery stenosis on renal parenchyma.

b) When parenchymal disease concurs to renal artery stenosis and causes a symmetrical increase in RRI values, scarce or no information can be obtained on the hemodynamic impact of arterial stenosis on renal parenchyma.

c) High asymmetric RRI values (≥0.80) distal to renal artery stenosis, with low interpolar diameter and volume of the ischemic kidney, are associated to bad outcome after revascularization.
d) In subjectcs with renal artery stenosis and high symmetric RRI values can be also the mirror of systemic rather than renal parameters; in these subjects the predictive role of RRI for good revascularization outcome is under debate.
In the absence of direct or indirect signs of renal artery stenosis, increases in the intraparenchymal RRI (RI > 0.75 e/o >0.80; PI > 1.50) associated with systemic atherosclerotic disease are indicative of microcirculatory damage related to nephroangiosclerosis or atheroembolic disease (1).

Conclusions

The use of RRI in clinical practice is limited by the incomplete knowledge of all renal and extra-renal pathophysiological determinants that can concur to modulate RRI value in a different way in different subjects. In acute conditions such as hydronephrosis and AKI, renal determinants have a major role and RRI can directly monitor renal damage. In vascular and parenchymal nephropathies, the role of renal and extra-renal determinants must be analyzed singly, according to the subject's clinical characteristics and questions put to RRI by the internist, who searches for an early marker of targeted organ damage in hypertension or diabetes, or for an independent predictor of renal and CV outcome (77).
To summarize, from the literature: a) In hypertensives with normal renal function and no albuminuria, RRI is an early marker of renal damage and could improve current clinical scores used to stratify early renal damage.especially in younger hypertensive and diabetics subjects. In older subjects RRI increases in accordance with the increase in systemic vascular stiffness and the role of renal determinants can weaken; because of this close relationship, RRI is also a marker of systemic atherosclerotic burden but the clinical relevance was not specifically investigated. b) In transplant kidney and in chronic renal disease high (>0.80) RRI values can mark renal damge and independently predict renal failure. c) Doppler ultrasound allows diagnosis and grading of renal stenosis in both fibromuscolar dysplastic and atherosclerotic diseases and can indirectly measure the hemodynamic impact of renal artery stenosis on the homolateral kidney. However, in elderly subjects with atherosclerotic renal artery stenosis coexisting renal diseases can independently increase RRI by the augmentation in renal vascular stiffness and tubulo-interstitial pressure and partially or completely hidden changes due to renal artery stenosis.

How and whether RRI assay could allow for improving the prediction of renal damage and of cardiovascular risk in asymptomatic subjects remains a matter of debate .

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Legends

Figure 1.RRI is measured by Doppler sonography in an intrarenal artery, as the difference between the peak systolic (PS) and end-diastolic (ED) blood velocities divided by the peak systolic velocity (PSV).

Figure 2. Different renal and extrarenal systemic determinants concur to determine RRI. 1a and 2a: renal and systemic determinants that decrease RRI. B: glomerular resistance scarcely or not affect RRI. 1c and 2c: renal and systemic determinants that increase RRI. Adapted by Boddi et al (21).

Figure 3. Schematic representation of possible 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 “tardus”, slow, and “parvus”, little pulsus;2) normal Doppler wave pattern and PSV/EDV at interlobar arteries ; 3,4) high RRI

(0.75-0.90) due to high peak systolic (PSV) and decreased end-diastolic velocity (EDV).Adapted by Boddi et al (21).

Figure 4.Schematic representation of Doppler flow patterns assayed at and distal to a hemodynamically arterial renal stenosis;RRI is lateralized (delta>0.05); when vascular or parenchimal nephropathies coexist, RRI values symmetrically increase and the hemodinamic effect of renal artery stenosis is hidden.Adapted by Boddi et al (21).

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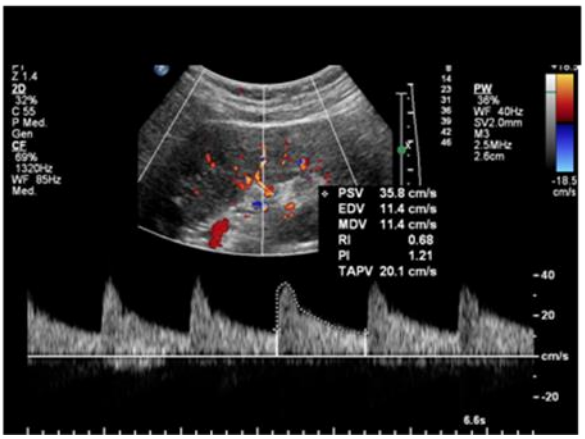
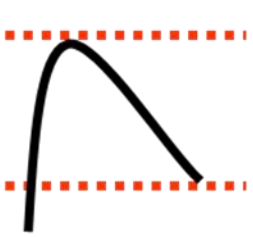
Figure 1





RRI=(PSV-PDV)/PSV

Renal determinants

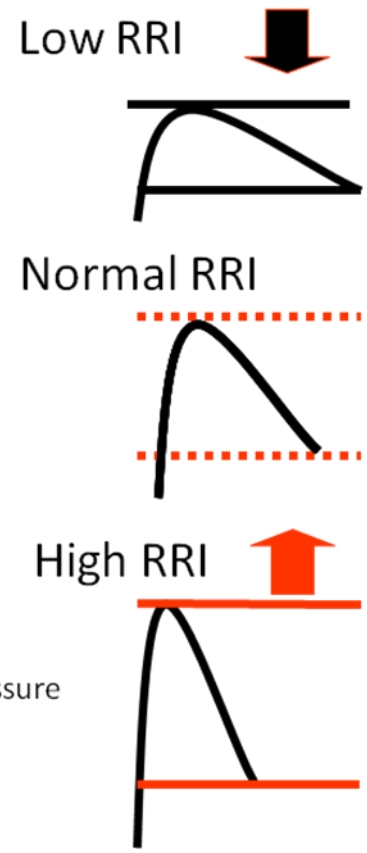
1a) >60% renal artery stenosis

b)

Glomerular vascular resistance scarcely affect RRI

1c)

Increased tubulo-interstitial pressure or renal venous pressure by hydronephrosis, AKI, abdominal hypertension, renal vein thrombosis



Systemic determinants

2a) Severe aortic valvular or aortic stenosis
Tachycardia,
Increased blood volume

2c)

Systemic adrenergic activation
Bradicardia
Increased systemic pulse pressure by aging,hypertension,diabetes

Figure 2

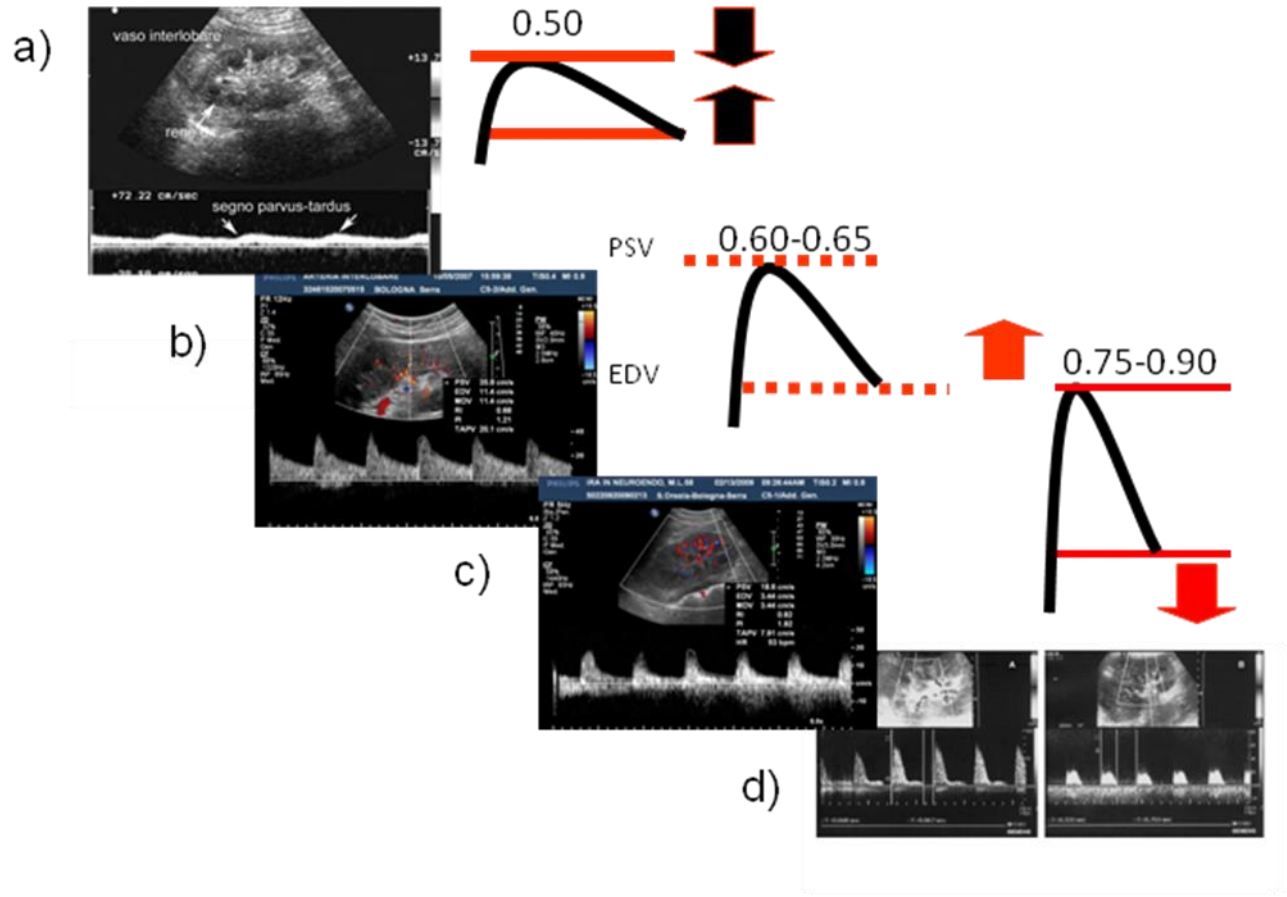
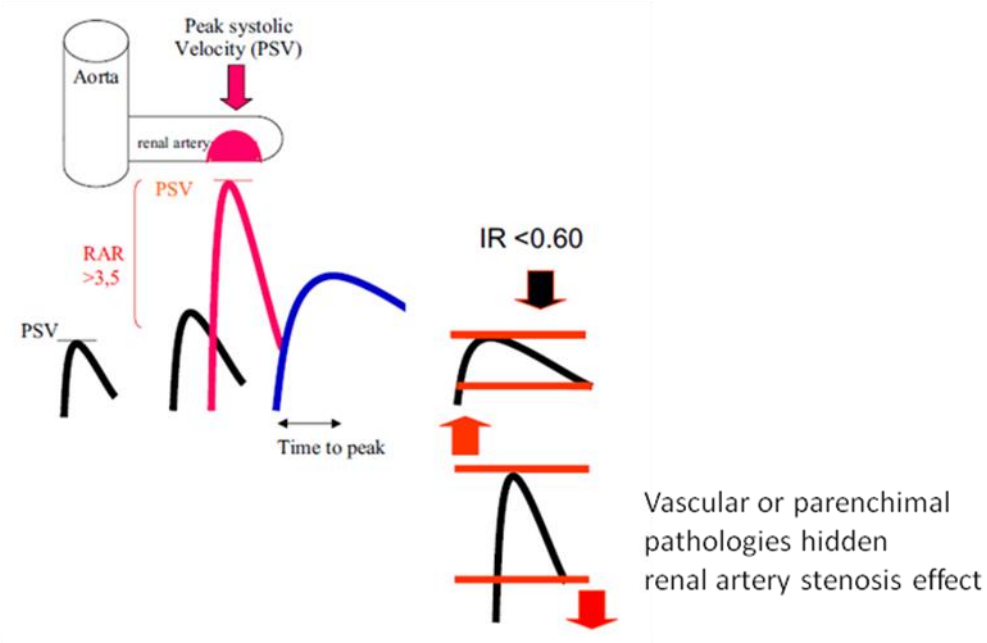

a)
vaso interlobare
segno parvus-tardus
0.50
b)
PSV
0.60-0.65
EDV
0.75-0.90
c)
d)

Figure 3

Figure 4


Peak systolic
Velocity (PSV)
Aorta
renal artery
PSV
RAR
>3,5
PSV
Time to peak
IR <0.60
Vascular or parenchimal
pathologies hidden
renal artery stenosis effect