Editorial

The "Renocentric Theory" of Renal Resistive Index: Is It Time for a Copernican Revolution?



Ultrasound (US) with duplex Doppler scanning has spread to the capillary level, becoming an irreplaceable tool in daily clinical practice thanks to its characteristics: low cost, repeatability, and noninvasiveness. Moreover, US has become over time more sensitive and accurate; it can be considered an extension of the clinician's hand. For this reason, it currently represents the ideal tool for first-level diagnostic use in several fields, and is the simplest and most flexible instrument for obtaining morphological and functional information on different organs, including the kidneys.

In this issue of *The Journal*, Gigante, *et al*[1] propose to assess renal involvement in patients with systemic sclerosis (SSc) through the evaluation of both structural and hemodynamic US measurements, paying particular attention to the Doppler-measured renal resistive index (RRI) and its clinical significance.

This index has a relatively recent history and an unfortunate name: *resistance index* (or *resistive index*). It was initially proposed by Gosling and King[2] and Pourcelot[3] in 1974 to identify the renal vascular diseases through the noninvasive measurement of intrarenal hemodynamics indirectly related to changes in arteriolar resistance. For a long time, the role of RRI has remained confined to renal damage, and it has been used as an important marker to predict the progression of renal function in patients with chronic kidney disease (CKD), diabetes mellitus, or hypertension (HTN). Its prognostic value has been studied only in the context of purely kidney diseases, with inconsistent results[4].

Over the years many authors have tried to find a correct interpretation of the RRI, and several studies have shown that it was minimally affected by intrarenal resistance: unexpectedly, the correlation between RRI values and changes in renal vascular impedance proved to be weak. Through *in vitro* studies, Tublin, *et al* observed that the RRI was dependent on vascular compliance rather than on intrarenal vascular resistance. It became less and less dependent on resistance as compliance decreased, and it was completely independent of vascular resistance when compliance was zero[5]. The same authors subsequently tried to assess the effect of acute changes in both renal vascular resistance (RVR) and pulse pressure on RRI measured by Doppler US in rabbit kidneys. Interestingly, when RVR increased 5-fold because of phenylephrine hydrochloride, the RRI changed only slightly, whereas the latter showed a stronger relationship with pulse pressure[5]. Unlike the common opinion based on theoretic considerations, the RRI was not effectively influenced by changes in intrarenal vascular impedance, and this revealed the need to reconsider the real role of RRI and to clarify the possible mechanisms underlying its modifications.

Based on this pioneering demonstration that the RRI is influenced by upstream factors rather than by merely intrarenal conditions, particular attention was subsequently paid by many authors to the possible relationship between RRI and markers of systemic vascular damage regardless of renal function or kidney impairment. Moreover, the growing interest of the scientific community in new potential markers associated with cardiovascular (CV) risk has put the RRI in a new role, similar to that assumed by other markers that are traditionally useful tools for CV risk stratification such as pulse wave velocity (PWV), carotid intima-media thickness, or albuminuria. This point of view is clear from the provocative way that Heine, *et al* entitled their article (2007): "Do Ultrasound Renal Resistance Indices Reflect Systemic Rather Than Renal Vascular Damage in Chronic Kidney Disease?"[6].

Several studies demonstrated a close link between RRI and PWV, a well-known risk factor strongly associated with CV morbidity and mortality and which represents a measure of arterial stiffness as well as an indirect expression of the elastic properties of the aorta. In 264 hypertensive patients with or without CKD, our research group demonstrated a significant positive relationship between the RRI and PWV

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regardless of renal function, and this close association remained statistically significant even after correction for various potentially confounding factors including glomerular filtration rate (GFR) and albuminuria[7].

This link can be easily understood if we consider the pathophysiology of hemodynamics and the physical factors that regulate it. The combined heart-arteries system can be compared to the "Windkessel model," according to which hemodynamic changes are caused by modifications of peripheral resistance or arterial distensibility: when peripheral resistance increases, the average pressure as well as both systolic and diastolic pressure increase, whereas the average pressure remains substantially unchanged when the arterial distensibility is reduced, despite an increase of pulsatile component with subsequent effect on pressure oscillations and pulsatory pressure. Increased arterial stiffness might therefore predispose the renal circulation to a greater hemodynamic burden (pulse more than mean arterial pressure), leading to higher RRI, itself an expression of renal pulsatile flow[7]. As suggested by Hashimoto and Ito, the connection between aortic stiffening and coexisting alterations in renal hemodynamics could be mainly imputed to the increase in aortic pulse pressure[8]. Moreover, it would be the pulsatile component of the pressure wave rather than the "static" one to stimulate the myogenic response of the glomerular afferent arterioles, thus causing an increase in renal vascular resistance[7].

Similarly, other markers of subclinical vascular damage also proved to be correlated with RRI, in particular carotid IMT, which represents an expression of atherosclerotic carotid disease and has already shown a close connection to systemic atherosclerosis and CV events. Many authors showed that carotid IMT was associated with renal hemodynamics in different populations[9,10], and our group demonstrated a strong association between RRI and severity of carotid atherosclerosis in subjects with or without CKD[11,12], thus strengthening the concept that RRI can be considered a marker of systemic vascular damage regardless of renal impairment. Moreover, increased RRI might reflect *in situ* structural damage of intrarenal vessels, conceivably mirroring systemic structural vascular changes. According to this hypothesis, histological studies conducted by Ikee, *et al*[13] showed that patients with higher RRI had hyaline changes, intimal thickening, and increased intima/media ratio of renal small arteries regardless of renal function, and other authors obtained similar results. Ikee, *et al* in their above-mentioned studies also reported a positive correlation between renal histopathologic findings of inflammation and RRI modification in patients with CKD[13]: the inflammatory state might determine endothelial dysfunction and it could promote development of atherosclerotic lesions and changes in endothelium-related regulation of intrarenal vessel motility. Similarly, the link between RRI and oxidative stress[14], an essential protagonist in the pathogenesis of atherosclerosis as well as in rheumatologic and CV diseases, could help to explain the association between renal hemodynamics and albuminuria, even in subjects with normal function. This correlation between micro- and macrovascular damage suggests the presence of a mechanism of dynamic integration between large arterial vessels and renal function, of which RRI is an important crossroads[15].

The transplanted kidney represents an excellent "human model" with which to understand the overall role of RRI as an expression of extrarenal vascular damage. In renal allograft recipients, Heine, *et al*[16] demonstrated that elevated resistance indices were associated with CV risk factors and with markers of systemic atherosclerotic disease in the recipient, but they were not independently associated with donor transplant function. Moreover, pathological characteristics (rejection) of the transplanted kidney did not always correlate with changes in RRI. Extrarenal upstream factors seemed to have a major effect on determining RRI, and the same authors suggested that RRI should not be considered specific markers of renal damage in transplant patients[16].

In line with these findings, the RRI proved to correlate with CV and overall mortality and to have a powerful prognostic value not only in patients with CKD or transplants[17], but also in subjects with normal renal function regardless of the CV risk category of the study population. In 426 essential hypertensive subjects, Doi, *et al* demonstrated that increased RRI was associated with an enhanced risk of CV and renal outcomes regardless of kidney function, and the combination of high RRI and low GFR exponentially and independently increased the risk of unfavorable events[18]. Other authors obtained similar results in different study populations, coming to overlapping conclusions[19,20].

Although most of these studies have been conducted mainly on populations with a traditionally recognized CV risk (HTN, diabetes, CKD, coronary artery disease), some authors have examined the role of RRI in different rheumatological diseases, stressing its role as a marker of renal damage and as a prognostic predictor of renal dysfunction. In 121 patients with SSc, Rosato, *et al*[21] observed an inverse association between GFR and RRI. Higher RRI values were found by Aikimbaev, *et al*[22] in progressive SSc patients with renal involvement compared to those without renal manifestations. Similarly, in patients with lupus nephritis, RRI was correlated with renal cortical fibrosis and other renal histologic findings[23]. However, systemic vascular damage was not evaluated in any of the above-mentioned studies, and it is well known that subclinical vascular changes are greater and more frequent in patients with renal impairment than in subjects with normal renal function. Moreover, renal damage can be an expression of systemic disease activity of rheumatological diseases, which often recognize an inflammatory pathogenesis and are associated *per se* with widespread vascular damage and increased CV risk. In line with this, several studies demonstrated that patients with SSc had early

structural and functional changes of atherosclerosis[24] as well as increased arterial stiffness[25], even in the absence of kidney damage. Similarly, it is widely known that patients with systemic lupus erythematosus (SLE) have more extensive vascular damage than healthy subjects[26].

It is therefore conceivable that increased RRI could be due to the vascular changes associated with systemic inflammation or with renal dysfunction rather than to the renal involvement *per se*. According to this hypothesis, in patients with SLE our group demonstrated that RRI was independently associated with IMT and aortic PWV also after adjustment for GFR, whereas SLE patients with normal IMT and PWV had RRI similar to healthy subjects[27]. Moreover, the evidence that RRI increased with progression of capillaroscopic damage and with presence of digital ulcers in subjects with SSc could represent further evidence of the systemic role of RRI[21].

As with other pathologic conditions, the "renocentric theory" of the RRI should therefore be dismissed when approaching rheumatologic disease, and it is desirable that RRI finds a broader use in clinical practice as an expression of systemic damage as well as a potential predictor of CV and overall mortality.

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