Systemic Arterial Hemodynamics and the "Renal Resistive Index:" What is in a Name?

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The renal resistive index (RRI), derived from the Doppler spectrum of intrarenal (segmental/interlobar) arteries, is defined as the dimensionless ratio of the difference between maximum and minimum (end-diastolic) flow velocity to maximum flow velocity:

$$\mathrm{RRI} = \frac{(\text{maximum velocity} - \text{minimum velocity})}{\text{maximum velocity}}$$

The RRI was initially proposed for the diagnosis of various forms of renal disease. One of the earliest prospective uses of the RRI was in the prediction of kidney function outcomes following intervention for renal artery stenosis.[1] In this study, an RRI >80 was associated with poorer outcomes, whether surgery or angioplasty was used to correct renal artery stenosis. However, accumulating evidence indicates that the RRI provides important information about the systemic vasculature as well. In this issue of *The Journal of Clinical Hypertension*, Calabia and colleagues add to our existing knowledge about the relationship between RRI and systemic arterial properties. The authors studied 202 hypertensive and 16 healthy adults and assessed the relationship between the RRI and various systemic arterial phenotypes, including carotid-femoral pulse wave velocity (a measure of large artery stiffness), pulse pressure, the aortic augmentation index (a surrogate of arterial wave reflections), 24-hour blood pressure (BP) measurements, ankle-brachial index, carotid intima-media thickness, and the presence of carotid plaques. They also assessed the relationship between RRI, classic cardiovascular risk factors, and circulating concentrations of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of endothelial nitric oxide synthase (NOS) that is independently associated with the presence of carotid atherosclerosis in the general population.[2,3] The authors found that RRI increases with age, serum creatinine, albuminuria, and diabetes mellitus and with increasing serum levels of ADMA. In multivariable analysis, greater RRI values were independently associated with increasing age, increasing hemoglobin A_{1c}, lower 24-hour diastolic BP, lower glomerular filtration rate, and greater carotid-femoral pulse wave velocity (or ambulatory arterial stiffness index). These findings add to the growing literature that demonstrates that the RRI is associated with aging, large artery stiffness,[4–8] BP variability,[9,10] and left ventricular remodeling and diastolic dysfunction.[11] The RRI is also associated with carotid atherosclerosis,[11] although whether this association is independent of large artery stiffness is unclear.

In order to interpret existing literature about RRI, it is essential to assess its hemodynamic determinants. This is a highly relevant issue, since it is often assumed that the RRI reflects properties predominantly of the renal vasculature, in particular, intra-renal vascular resistance, as its name would indicate. Indeed, in many papers, the terms resistive index and renal vascular resistance are used interchangeably.[4,7–10] Under the assumption that RRI is indeed a measure of intra-renal vascular resistance, associations reported by Calabia and coworkers and others could be interpreted as supportive of a relationship between the large arteries and the small renal vessels. However, strong evidence exists demonstrating that the RRI has hemodynamic determinants different from intra-renal vascular resistance, and that the latter has little influence on the RRI within physiologic ranges.[12,13]

In vitro experiments showed that the RRI is dependent on vascular compliance and resistance, becoming less and less dependent on resistance as compliance decreases, and being completely independent of vascular resistance when compliance is zero.[12] In a different set of experiments, rabbit kidneys were perfused ex vivo using a pulsatile perfusion system in which renal vascular resistance and systolic, diastolic, and pulse pressure were controlled.[13] In these experiments, the RRI increased only with marked, likely nonphysiologic, increases in renal vascular resistance. Indeed, changes in the RRI in response to marked renal vasoconstriction were only marginally greater than RRI measurement variability. However, the RRI was markedly affected by changes in pulse pressure. These in vitro and ex vivo experiments above are supported by in vivo experiments and human observations. Using an infusion of L-NG-monomethyl arginine (L-NMMA), which, like ADMA, is an inhibitor of endothelial NOS, Raff and colleagues showed that neither baseline nor the changes in RRI were correlated with renal vascular resistance or renal perfusion, assessed with para-aminohippuric acid and inulin clearance.[14] In contrast, RRI correlated with central pulse pressure at baseline and during L-NMMA infusion, whereas renal vascular resistance did not correlate with central pulse pressure. Studies in kidney transplant recipients in which a consistent relationship

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DOI: 10.1111/jch.12276

between RRI and (recipient) pulse pressure has been demonstrated, further support the importance of systemic arterial factors in the RRI.[6,15]

The importance of systemic arterial hemodynamics as determinants of the RRI can also be inferred from analysis of the formula used to derive it. It can be seen from this formula that, for any given maximum systolic velocity, the RRI increases as the end-diastolic flow velocity decreases. The end-diastolic flow velocity is, in turn, a function of the intra-renal vascular resistance (which tends to reduce renal blood flow velocity) and the end-diastolic pressure in the systemic arterial tree (which directly promotes flow across the renal resistance, thus increasing the flow velocity). This means that, for any given intra-renal vascular resistance, a lower diastolic BP will reduce blood flow, thus increasing the RRI. This is consistent with the findings of Calabia and colleagues, which demonstrate a negative independent correlation between 24-hour diastolic BP and the RRI in multivariable analyses. Moreover, this concept is not unique to end-diastole and also applies to systolic velocity. Analogous to diastolic arterial pressure influencing end-diastolic renal artery flow velocity, systolic (peak) arterial pressure promotes a greater peak flow across the renal vascular resistance, thus increasing peak flow velocity. To the degree that, for any given intra-renal vascular resistance, the maximum and minimum velocities used in the RRI computation are a direct function of arterial peak and end-diastolic pressure, it is expected for the RRI to be correlated with systemic arterial pressures. Indeed, in the isolated rabbit kidney studies mentioned above, a linear relationship was reported between the "pulse pressure index" (systolic pressure – diastolic pressure/systolic pressure) and the RRI. To the degree that arterial stiffness increases pressure pulsatility in the aorta, it will also be expected to affect the RRI via its hemodynamic consequences (increased pressure pulsatility), without implying abnormalities in intra-renal resistance. The correlation between RRI and microalbuminuria (demonstrated by Calabia and associates, as well as previous reports),[11,16] is often cited in support of the RRI reflecting intra-renal microvascular properties. However, this may be an epiphenomenon, reflecting the effect of increased pulsatility in the aorta, which, in turn, may lead to greater microvascular damage over time.

Although it is clear from these studies that the RRI reflects predominantly systemic vascular conditions, regardless of the presence of a structural or dynamic change in intra-renal vessels (its name being misleading in most circumstances), it is also clear that under some circumstances, it can be directly affected by renal disease, such as in conditions characterized by increased renal interstitial pressure, urinary tract and intra-abdominal pressure, and allograft rejection.[15,17] Therefore, the interpretation of the RRI, like any other physiologic index, should carefully take into account the clinical or research context in which the measurement is made. In the context of hypertension, we should carefully acknowledge that the RRI is thus not necessarily a marker of the status of the renal microcirculation but may rather represent ongoing systemic arterial hemodynamic phenomena that may lead to progressive renal damage over time. Studies such as the one by Calabia and colleagues support the need for prospective studies to test this hypothesis.

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