Editorial Commentary

Why Does Renal Resistive Index Predict Mortality in Chronic Kidney Disease?

Rajiv Agarwal

See related article, pp 382–388

Chronic kidney disease (CKD) is an important public health problem because it is common, expensive, and is associated with a high burden of morbidity and mortality. Although some people with CKD will progress to end-stage renal disease (ESRD), more commonly they die before they reach dialysis. The major cause of death is cardiovascular, but it is now being increasingly recognized that compared with the general population, infection-related and cancer-related deaths are also tremendously elevated in people with CKD. Many risk factors are associated with death in people with CKD but the search for prognostically important risk factors continues. Ultrasound evaluation of the kidneys is an important part of the evaluation of the patient with CKD and prognostic markers derived from this commonly performed test have received little attention.

One such ultrasound-based measurement that is potentially useful for the evaluation of a variety of acute and CKDs is called the renal resistive index (RRI). RRI is obtained using a pulsed-wave Doppler sample volume in the distal intrarenal vessels such as the arcuate arteries (at the corticomedullary junction) or interlobar arteries (along the border of the medullary pyramids) to calculate the peak systolic velocity and the end diastolic velocity. RRI is calculated as the ratio of peak systolic velocity minus minimum diastolic velocity to peak systolic velocity. An elevated RRI may indicate either an elevated renal vascular resistance or an impaired vascular compliance.

In this issue of Hypertension, Navaneethan, who led a collaboration of individuals from quantitative health sciences, cardiovascular medicine, and nephrology from the Cleveland Clinic, reports the prognostic value of RRI in an important cohort study. In this cohort study, enrolled from an electronic registry of patients with CKD were 1962 individuals seen at the Cleveland Clinic who had stage 3 to 4 CKD and also had the absence of renal artery occlusion of ≥60%. All participants had RRI measured. After a median follow-up of 2.2 years, 428 patients died. The large number of patients allowed Navaneethan’s group to examine the independent determinants of RRI and, more importantly, the large number of deaths allowed the independent association of RRI with all-cause mortality.

It is important to note that patients with evidence of renal artery stenosis were excluded because including these patients would have confounded the results; earlier studies have indicated that compared with controls those with significant renal artery stenosis have a lower RRI. It is not surprising that an abnormal test result defined as RRI ≥0.70 was independently associated with an older age, diabetes mellitus, coronary or peripheral vascular disease, and elevated systolic blood pressure. The independent association of RRI with greater use of β-blockers may have been because of reduced heart rate and prolonged diastole allowing the diastolic Doppler velocity to fall to a smaller fraction of the systolic velocity compared with patients who were not receiving the drug. As compared with men, a higher RRI among women was a novel finding. More importantly, compared with those with RRI <0.70 those with RRI ≥0.70 had a lower estimated glomerular filtration rate (eGFR; 38.7 versus 40.6 mL/min per 1.73 m²; P<0.001), but this relationship with eGFR was not seen in the multivariate analysis. Thus, an elevated RRI, among those with CKD, is not simply because of a lower eGFR.

The adjusted hazard ratio (HR) for all-cause mortality was 1.29 (95% confidence interval, 1.02–1.65). This HR seems robust because it was adjusted for missing data (multiple imputation adjusted HR). Because the HR was also adjusted for many other variables that are associated with increased mortality such as age, sex, blood pressure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and congestive heart failure, these epidemiological data assert a strong association between RRI and all-cause mortality. Furthermore when RRI was used as a continuous variable, it was also associated with all-cause mortality implying a linear relationship between the 2.

The reasons for the strong relationship between RRI and mortality remain unknown but common pathophysiological mechanisms that associate with death may also increase RRI (Figure). Because RRI can be elevated because of either reduced vascular compliance or an increased renal vascular resistance, pathways that alter vascular compliance or resistance and also known to increase mortality are discussed further.

First, an elevated RRI is associated with poor vascular compliance or its common clinical manifestation, an elevated pulse pressure. It may seem surprising that in comparison with the compliance of the renal circulation, the compliance of the systemic circulation seems to be of greater importance in altering RRI. However, this is evident from
studies of RRI in transplanted kidneys. In such kidneys, the RRI of the donor kidney correlates more, not with the age of the donor, but with the age of the recipient.\(^{11}\) The poor vascular compliance heightens the peak systolic pressure which when transmitted to the microcirculation causes damage to the capillary bed and leads to adverse downstream events including progression to ESRD and death. However, progression to ESRD may not be sine qua non to death. In fact, among transplant patients, RRI \(\geq 0.80\) at 3, 12, and 24 months after transplantation was strongly associated with death (HR, 5.20 at 3 months; 3.46 at 12 months; and 4.12 at 24 months) but not so with the need for dialysis or \(\geq 50\%\) reduction in eGFR.\(^{11}\) Thus, an elevated RRI may indicate factors outside the kidney, such as arteriosclerosis, that culminate in death. However, arteriosclerosis is only 1 such factor. In the current study, the Cox model for all-cause mortality and RRI was simultaneously adjusted for systolic and diastolic blood pressure. This in effect accounts for pulse pressure and suggests that RRI is of prognostic value above and beyond pulse pressure, a proxy for arterial stiffness.\(^{6,10}\) Thus, other factors beyond arteriosclerosis must be important in mediating the relationship between RRI and mortality. Second, an elevated RRI may indicate high renal vascular resistance and low renal blood flow. Although there are good reasons to question the validity of the relationship of RRI with renal vascular resistance,\(^{6,8,10}\) those with elevated RRI may be those with greater microvascular disease. In this context, elevated RRI may indicate disease specific to the tubulointerstitial compartment. At least 3 studies support this hypothesis. First, in a study of 41 patients who had simultaneous kidney biopsy and evaluation of RRI in both kidneys, those with tubulointerstitial nephritis (n=16) had mean RRI of 0.73; 75% of these kidneys had RRI \(\geq 0.7.\)\(^{12}\) This was significantly higher in comparison with those patients who had disease limited to the glomerulus (RRI, 0.58). Second, in a much larger study of 992 patients from China who had simultaneous assessment of RRI and kidney biopsy, the tubulointerstitial damage score was one that was the most strongly associated with RRI.\(^{13}\) Third, kidney biopsies performed among transplant patients because of graft dysfunction demonstrated that among such patients those with a histological diagnosis of acute tubular necrosis had a significantly higher RRI than patients with normal histological findings at the time of such a biopsy (0.86±0.09 versus 0.78±0.14; \(P=0.007\) ).\(^{11}\) It is now well recognized that tubulointerstitial changes are the strongest determinant of progression to ESRD;\(^{14}\) those with ESRD also have a high risk for mortality. RRI may simply detect this phenomenon noninvasively.

In summary, the study by Navaneethan’s group has discovered a biomarker that is kidney specific and predicts death among patients with CKD, independent of many other risk factors. The fact that it uncovers this independent risk in younger people and those with an earlier stage of kidney disease (CKD stage 3) makes this marker even a more exciting discovery. Before we can use this marker for individual level prediction of death several steps will need to be taken, such as: (1) validation in other cohorts of patients with CKD; (2) adjustment for albuminuria as a predictor of outcomes while evaluating the incremental value of this marker over and above other risk factors; (3) assessing the change in RRI and subsequent deaths; and (4) assess the competing risks of ESRD and death among such patients. The latter may be particularly useful as it may further shed light on the potential pathophysiological and prognostic significance of this important noninvasive and widely available test.\(^{15}\) Finally, of great interest would be pathophysiological experimental studies that interface radiologists, nephrologists, physicists, and those in the quantitative sciences to better understand the pathophysiological basis of alterations in RRI. Such collaborations may yield further refinement of this valuable tool.

\[\text{Figure. Pathophysiological pathways that elevate renal resistive index and also increase the risk for death. Reduced vascular compliance (1) and an increased renal vascular resistance (2) increase renal resistive index. Arteriosclerosis increased the risk of death and reduces vascular compliance. A reduced capillary surface area results in constrained area of the vascular bed culminating in increased vascular resistance. Tubulointerstitial disease reduces the size of the vascular bed and associates with end-stage renal disease (ESRD) and death. See text for detailed explanations.}\]
Sources of Funding
Dr Agarwal is supported by a grant from VA Merit Review.

Disclosures
Dr Agarwal has consulted for the following companies: Merck, Novartis, Daiichi Sankyo, Takeda, Abbvie, Astra Zeneca, and Johnson&Johnson.

References
Why Does Renal Resistive Index Predict Mortality in Chronic Kidney Disease?
Rajiv Agarwal

_Hypertension_. 2015;66:267-269; originally published online June 15, 2015;
doi: 10.1161/HYPERTENSIONAHA.115.05690

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/66/2/267

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/