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Review Article

Atherosclerotic renal artery stenosis in the post-CORAL era part 1: the renal penumbra concept and next-generation functional diagnostic imaging

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Abstract

After three neutral trials in which renal artery stenting failed to improve renal function or reduce cardiovascular and renal events, the controversy surrounding diagnosis and treatment of atherosclerotic renal artery stenosis and renovascular hypertension has led to paradigm shifts in the diagnostic algorithm. Noninvasive determination of earlier events (cortex hypoxia and renal artery hemodynamic changes) will supersede late sequelae (calcific stenosis, renal cortical thinning). Therefore, this review proposes the concept of renal penumbra in defining at-risk ischemic renal parenchyma. The complex field of functional renal magnetic resonance imaging will be reviewed succinctly in a clinician-directed fashion. J Am Soc Hypertens 2016;10(4):360–367.

Keywords: Atherosclerosis; cardiovascular diseases; radiology; renovascular hypertension.

Introduction

Over 72 million Americans have hypertension, at least 5% of which is estimated to be renovascular hypertension (RVH) secondary to atherosclerotic renovascular disease (ARVD).[1] The 7% of the American population aged more than 65 years with ARVD has a markedly elevated cardiovascular risk.[2] Moreover, the condition is far reaching, with ARVD affecting nearly 5% of patients with chronic renal insufficiency, nearly 20% of incident dialysis patients, nearly 35% of patients with congestive heart failure, and nearly 50% of patients with diffuse atherosclerosis.[3,4] However, the medical community has yet to unify around a consistent clinical approach that best serves the unmet needs of these patients. Specifically, recovery of renal function has not yet been consistently demonstrated with any of the available clinical approaches (possibly due to relatively late detection along the natural history of this disease process).

Observational data sets have conflicted with randomized controlled trials (RCTs) regarding renal artery stenting outcomes for either RVH or ARVD with or without chronic kidney disease. Stenting was not superior to best medical therapy in the major RCTs (Cardiovascular Outcomes in Renal Atherosclerotic Lesions [CORAL],[5] Angioplasty

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and Stent for Renal Artery Lesions [ASTRAL],[6] and Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery [STAR][7]). As a result, the enthusiasm for renal artery stenting has decreased just as the availability of trained professionals and technology has reached maturity.

However, there are data pointing to beneficial effects of successful renal artery stenting. Although the literature has not shown stenting to help ''all-comers'' with ARVD, poststent improvement in renal function is a long-term predictor of survival for these patients.[8]

Stenting trials have actually failed their mission of in-depth studying renal artery stenting. The inclusion and exclusion criteria used were questionable. Angiographic pressure measurements provide an established definition of a hemodynamically significant atherosclerotic lesion and should serve this control role in RCTs of renal artery stenting.[9] Moreover, CORAL changed its inclusion criteria mid-study to include patients who are less likely to benefit from stenting, by shifting from systolic hypertension greater than 155 mm Hg on two medications to simply a glomerular filtration rate (GFR) <60 mL/min regardless of hypertension.[5]

Exclusion criteria have failed as well, as renal artery stenting RCTs excluded[9] those patients who have clearly benefitted most from transcatheter intervention, namely the high-risk clinical syndromes such as flash pulmonary edema or circulatory congestion, deteriorating kidney function, and hypertensive urgency.[9] Beyond this, trials such as ASTRAL used investigator-reported angiographic data without central core laboratory control (the latter being implemented in CORAL), which is subject to bias and inaccuracy, and falls below the quality control measures used by the United States Food and Drug Administration (FDA).[9,10]

Our approach to revascularization thus far may not be sufficiently early in the natural history of renovascular disease. Furthermore, relaxed enrollment criteria of the major stenting trials likely enrolled patients with incidental renal artery stenosis, not actual RVH. Mounting basic science evidence regarding RVH purports an ischemic-inflammatory cascade that creates irreversible cortical damage via oxidative stress injury, vascular rarefication, and the recruitment of profibrotic mediators.[11] However, we currently do not have methods for imaging or measuring this natural history and thus determining which patients have ''reversible'' ARVD amenable to revascularization. The stenting literature has enrolled patients who may have been at different stages (early versus late) in this natural history, and if so, this lead time bias alone could explain the disparate and inconsistent blood pressure and kidney function responses that have been documented in the stenting literature. Furthermore, there is a possibility of reperfusion injury post-revascularization mediated by oxygen free radicals. If this risk can be evaluated pre-procedure, then interventions to mitigate reperfusion injury can be developed and implemented.[12]

Therefore, a new approach for imaging, medical management, and transcatheter therapy is needed. This review focuses on imaging techniques to improve patient selection and addresses the following questions: is there a basic science rationale for imaging in renovascular disease? What is the optimal imaging work-up for patients with ARVD? Is there a consensus pathologic and radiologic definition for renal penumbra? What next-generation imaging modalities are envisioned for this population?

What Is the Basic Science Rationale for Imaging in RH and ARVD?

The ''clinical'' premise of basic radiologic imaging is that static anatomic features will influence management decisions. However, clinical validation of modern imaging biomarkers has lagged because imaging of the renal artery and renal parenchyma remains inconsistently used in a radiologist-dependent, referrer-dependent, and institution-dependent fashion. For example, a renal cortical thickness of less than 8 mm has been proposed as a diagnostic criterion for RVH secondary to ARVD,[13] although we know that poststenotic kidneys with normal cortex thickness can have markedly reduced renal function as measured by isotope renography, and there are other potential causes of reduced cortical thickness.[14] Gross anatomic measurements (eg, kidney length) may oversimplify RVH and disregard important physiologic criteria for critical ARVD, such as, for example, renal function stability or improvement after withdrawal of renin-angiotensin system blockade.[15]

Angiographic criteria for a ''hemodynamically significant'' lesion have remained at 70% stenosis, although a 10 mm Hg pressure gradient is a more exact definition.[16] Intravascular pressure measurements are invasive procedures (only performed if there is an intent to intervene) exposing to renal artery angiogram (contrast nephropathy) and catheterization (dissection, cholesterol embolism) potential complications, time consuming, and require special equipment, which partially explains why the practice has not (yet) universalized and why they were not incorporated in the CORAL trial.

In short, the rationale for imaging is shifting from grading late sequelae (stenosis, atrophy, cortical thinning) to grading earlier events (cortex hypoxia, stenotic pressures). This is because we increasingly understand that the kidneys adapt to moderate decreases in arterial inflow without experiencing ischemia, possibly through mechanisms such as nitric oxide production which has been shown to maintain oxygen tension in the clipped kidney of a 2-kidney 1-clip Goldblatt hypertensive rat model.[17] This ischemic adaptability has been observed by blood-oxygen -level–dependent (BOLD) sequence magnetic resonance imaging (MRI) scanning.[18] Modern imaging has