PERSPECTIVES IN HYPERTENSION

Diagnosis and treatment of renal artery stenosis

PETER W. DE LEEUW AND ABRAHAM A. KROON

Department of Medicine, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands

Whenever we are confronted with a newly referred patient with hypertension, the question comes up whether we should look for the presence of renal artery stenosis, and if we find one what we should do about it. Although our clinic has treated hypertensive patients with renal artery stenosis for decades, questions about the most appropriate diagnosis and treatment persist.

In our experience, most cases of renal artery stenosis are atherosclerotic in origin but in recent years we have seen an increasing number of patients with fibromuscular dysplasia (FMD), probably because of greater awareness among clinicians of this condition (**figure 1**). Studies have shown that these two forms of renal artery stenosis do not share common pathophysiological mechanisms. Whereas in atherosclerotic renal artery stenosis (ARAS), flow disturbances and intrarenal inflammatory processes play a paramount role, the kidney of patients with FMD is relatively spared and resembles more the kidney of patients with primary hypertension.[1] In this short overview, we will focus primarily on ARAS.

Diagnosis of renal artery stenosis

When do we have to suspect the presence of renal artery stenosis and how should we shape the diagnostic process? Roughly speaking, the main clinical features a patient with renal artery stenosis may present with are resistant hypertension, ischemic nephropathy or so-called cardiac destabilization syndromes as 'flash' pulmonary edema, recurrent episodes of heart failure and acute coronary syndrome. Sometimes an abdominal bruit or unexplained hypokalemia may alert the physician that renal artery stenosis may be present. Overall, laboratory examination is unremarkable in patients with FMD but in the case of ARAS, one may find a reduced estimated glomerular filtration rate (eGFR) and/or urinary albumin loss. Recently, we evaluated in our clinic whether certain clinical

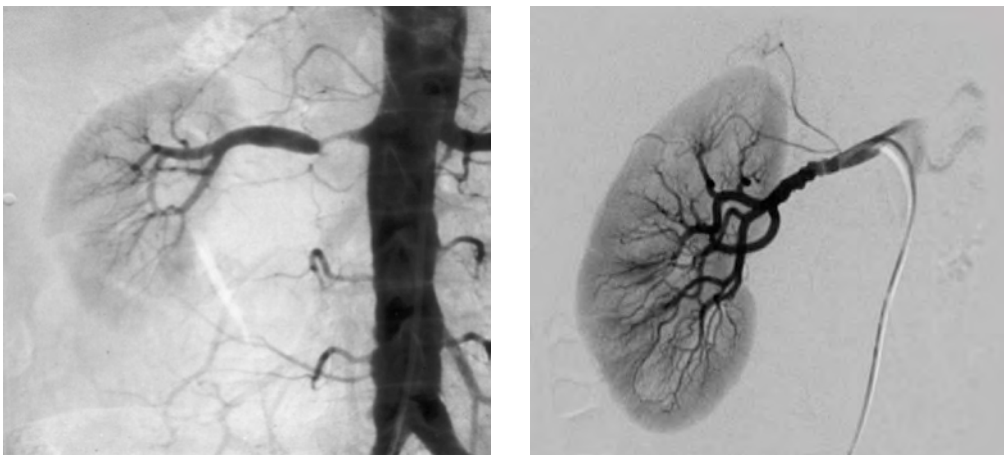

Figure 1: Examples of atherosclerotic renal artery stenosis (left) and fibromuscular dysplasia (right). Authors' series.

clues and patient characteristics could predict the results of renal angiography. Most clues had only limited predictive value because of low prevalence, lack of discriminative ability or lack of additional information over and above other patient characteristics. Only three clues (a length difference between kidneys of 10% or more, the presence and extent of extra-renal atherosclerosis, in particular peripheral artery disease, and recent onset of hypertension), proved to be independent predictors (unpublished data). However, patients can also be completely symptomless. Thus, when clinical suspicion is high, we still have to ascertain whether a stenosis is present and whether the stenosis is hemodynamically, or even more importantly, clinically significant.

In essence, we have four diagnostic modalities to screen for stenotic lesions in the renal artery: duplex ultrasound (DUS), magnetic resonance angiography (MRA), computed tomography angiography (CTA) and digital subtraction angiography (DSA). **Table 1** summarizes some of the advantages and limitations of each of these modalities.[2] Clearly, these techniques provide only information on anatomical lesions of the renal arteries and do not tell us anything about the clinical significance of the abnormality. Even DUS lacks enough sensitivity and specificity to fulfill such a role.

Unfortunately, there are as yet no reliable tests or biomarkers to differentiate between true renovascular hypertension from ARAS secondary to hypertension or from hypertension and ARAS being totally unrelated.

Treatment of renal artery stenosis

While the diagnosis of renal artery stenosis is already problematic for the clinician, decisions regarding treatment are even more so. In essence, there are three options: surgery, percutaneous transluminal renal angioplasty (PTRA) with or without stenting and medical treatment. With the advent of PTRA, the surgical approach has faded into the background. There is only one randomized study which compared PTRA to a surgical approach and by and large, this trial did not find significant differences in outcome after the two treatments.[3] However, after PTRA had become the treatment of choice, trials which compared the effect of PTRA with or without stenting on top of medical treatment to that of medical treatment alone failed to show any appreciable benefit of angioplasty. Several meta-analyses of those trials came to the same conclusion. The most recent, updated meta-analysis comes from a group of Japanese and American researchers.[4] They scrutinized the trials with respect to cardiovascular disease (CVD)-related mortality, the incidence of CVD events, suppression of renal function decline, changes in blood pressure, changes in the number of antihypertensive drugs and serious adverse events. Based on the data of 2275 patients from nine randomized controlled trials they concluded that there were no significant differences between medical therapy alone and the combination of medical therapy and PTRA with respect to any of the outcome measures except for the number of antihypertensive drugs. Combination therapy reduced this number by 0.42 (95% confidence interval: 0.12-0.71) which, although significant, is not very impressive. Additionally, they noted

Table 1. Diagnostic modalities to detect renal artery stenosis.

Test	Advantages	Limitations
Duplex ultrasound	Noninvasive, radiation-free, cheap, also applicable in patients with reduced renal function or contrast allergy.	Time consuming, highly operator-dependent, difficult in obese patient or distended bowel gas.
Computed tomography angiography (CTA)	Excellent special and temporal resolution of renal arteries and surrounding structures.	Use of iodinated contrast and ionized radiation. Severe renal artery calcification may obscure luminal narrowing.
Magnetic resonance angiography (MRA)	High-quality noninvasive anatomic images of the renal arteries and surrounding structures.	High cost, contraindicated in patients with ferro-magnetic implants and those with eGFR < 30 ml/min.1.73m^2, when using group 1 gadolinium-based contrast.
Digital subtraction angiography (DSA)	Direct hemodynamic measurements and if needed, revascularization could be performed immediately.	Use of iodinated contrast and ionized radiation. Invasive modality. Pre- or posthydration when eGFR < 30 ml/min.1.73m^2

Adapted from Bavishi et al.[2] eGFR: estimated glomerular filtration rate.

that the included studies demonstrated a low-to-moderate risk of bias, high heterogeneity and limited overall quality.

It is striking that almost all authors who have criticized the trials for methodological reasons state that the number of patients with advanced disease are underrepresented in these trials while in their opinion such patients are likely to benefit most of angioplasty. This is a rather curious reasoning. It makes much more sense to suppose that PTRA will help patients with less advanced disease. Indeed, already from an early phase of stenosis intrarenal abnormalities develop.[5] Unfortunately, no trials have examined the effect of angioplasty specifically in patients with low-grade renal artery stenosis.

Currently, there is a tendency to restrict a dilation procedure to patients who exhibit a significant pressure gradient across the stenosis, either at baseline or after a hyperemic stimulus.[6] It should be stressed, though, that there is no evidence yet for better outcome when treatment decisions are based on functional measurements such as pressure gradients or fractional flow reserve.[7]

In a joint venture, a consensus panel of the Society for Cardiovascular Angiography and Interventions (SCAI), the American Heart Association (AHA) and the American College of Cardiology (ACC) has formulated criteria for 'appropriate use' of angioplasty in patients who are most likely to benefit from this procedure.[8] Cardiac destabilization syndromes, rapidly deteriorating renal function or stage IV chronic kidney disease in patients with treatment-resistant hypertension and bilateral renal artery stenosis or stenosis in a solitary kidney are considered appropriate indications. Newly discovered hypertension or asymptomatic ARAS are not. In all other cases, it should be left to the professional judgement of the clinician. It should be stressed, though, that these recommendations are based on expert opinion and not on hard evidence. Irrespective of whether angioplasty is considered or not, in patients with ARAS cardiovascular risk management (statins, antiplatelet therapy) is always indicated.

In patients with FMD, the therapeutic approach is a little different. In the absence of concurrent atherosclerotic lesions, anti-atherosclerotic measures are not useful in FMD. Especially in patients younger than 50 years, one may consider angioplasty[9] but there have been no randomized trials of PTRA in FMD.

We must conclude that we can still not make recommendations for the diagnosis and treatment of renal artery stenosis that are based on sound and irrefutable clinical evidence. Probably our best options today are to screen for a stenosis with CTA, to confirm the diagnosis with DSA and to base the decision to do angioplasty on individual clinical grounds.

Peter W. de Leeuw – p.deleeuw@maastrichtuniversity.nl

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