European Society of Hypertension Scientific Newsletter:
Update on Hypertension Management

2007; 8: No. 5
revised version

HOW TO HANDLE RENOVASCULAR HYPERTENSION

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Renovascular hypertension (RVH) is defined as the elevation of arterial pressure precipitated by a haemodynamically significant stenosis of a renal artery or arteries (that is, a stenosis greater than 75% of the vessel lumen or 50% with post-stenotic dilation). When the lesion affects both renal arteries, or a single functioning kidney, and is accompanied by renal failure (plasma creatinine concentration above 1.5 mg/dl), it is called ischemic nephropathy or ischemic renal disease [1, 2].

The rate of renovascular hypertension is less than 1% when a mild--moderate hypertension population is assessed, but this increases according to the severity of the hypertension and with population age [3].

Two well-differentiated of renal artery lesions have been described. Fibromuscular dysplasia is a non-inflammatory lesion that affects young women between 15 and 20 years of age, and its incidence is less than 10% of all RVH cases. Progression of lesions from the angiographic point of view is defined by the appearance of new focal lesions, or a worsening of the existing stenosis grade, and is produced when the intima layer of the artery is affected [4–5].

The most prevalent mechanism underlying lesion of the renal arteries (90%) is atherosclerosis. This increases with age, especially in elderly patients with diabetes, hyperlipidaemia, aortic occlusive disease and lesions in the coronary artery. Atherosclerosis of the renal artery is a progressive disease that may cause ischemic renal disease, also known as ischemic nephropathy. The prevalence of ischemic nephropathy is poorly quantified, and may vary from 30% in patients with coronary disease to 50% in those with diffuse arteriosclerotic disease [5]. It has been estimated that it may be responsible for 5% to 22% of cases of end-stage renal failure in dialysis programs [6].

Diagnosis

The signs and symptoms that suggest RVH include sudden onset of hypertension, especially in young women (fibrodysplastic lesions), existence of hyperkalaemia, abdominal vascular murmurs and asymmetry in renal size (> 1.5 cm) according to ultrasonography criteria. When the lesion is due to atheroma plaque in the ostium of the renal artery it affects men over the age of 60 and is accompanied by lesions in other vascular territories. Table 1 shows the most frequent clinical characteristics according to our experience [7–9] in renal arterial lesions due to atherosclerosis.

Screening tests

According to the recommendations of the American College of Cardiology/American Heart Association [10], the following techniques are recommended:

- **duplex Doppler ultrasonography:** in addition to evaluating renal size, it also assesses the morphology of the renal artery and the characteristics of intrarenal flow. In experienced clinical centres, sensitivity and specificity of this test may exceed 96% [11]. Measurement of the intrarenal resistance index (IRI) is an indirect evaluation of the integrity of the circulation of intrarenal vessels and intraparenchymatous lesion. IRI values greater than 0.80 indicate severe parenchymatous disease and reveal little clinical benefit in the control of blood pressure and recovery of kidney function if revascularization is performed;
- **magnetic resonance angiography (MRA):** The test specificity increases with three-dimensional MRA with gadolinium. The sensitivity and specificity of the technique are 97% and 93%, respectively, in the diagnosis of stenosis greater than 50%. In recent months, a serious disease called Nephrogenic Systemic Fibrosis [12], secondary to the administration of gadolinium, has been described in some patients with severe kidney failure;

Table 1. Clinical findings consistent with atherosclerotic renal artery stenosis

Abrupt onset at age > 60 years old
Severe hypertension
Smoking
Occlusive vascular disease (cerebrovascular, coronary, peripheral)
Abdominal bruit, flank bruit or both
Unexplained azotaemia
Azotaemia induced by treatment with ACEI/ARB
Flash pulmonary oedema

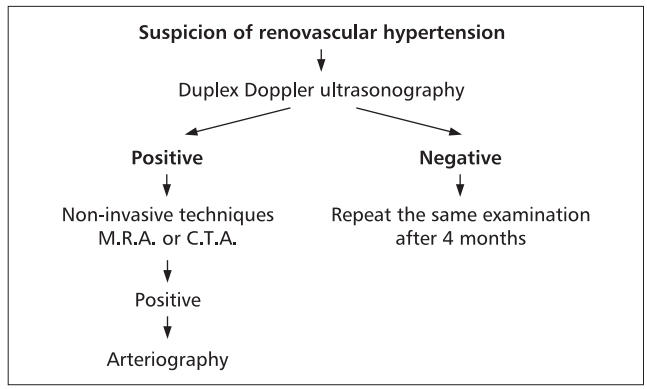

Figure 1. Algorithm for the diagnosis of patients with renovascular hypertension

- **spiral computed tomography angiography (CTA):** The sensitivity of this method varies from 67% to 92% and can be improved to 98% with a specificity of 84%, by using three-dimensional techniques and projections with maximum intensity. The need to administer 100 to 150 ml of iodine contrast may cause nephrotoxicity in patients with kidney failure;
- **renal arteriography:** This is the technique used most often to obtain a clear confirmation of renovascular hypertension, and an angioplasty can be performed if indicated at the same time. It has the disadvantage of being an invasive technique with possible complications due to the iodine contrast and due to the risk of atheroembolism.

Figure 1 shows the algorithm for the diagnosis of patients with renovascular hypertension.

Other screening tests

Renal scintigraphy following ACE inhibitor: The sensitivity and specificity of this test are 78–90% and 88–98%, respectively. This decreases when the lesion is bilateral and in kidney failure. In patients with ischemic nephropathy, only renal scintigraphy is used to demonstrate kidney viability.

Renal vein renin measurements: This is used on rare occasions in patients with lesions in both renal arteries.

The different diagnostic techniques mentioned have been compared in a meta-analysis of 55 studies in patients evaluated with RVH [13]. MRA and CTA examinations gave the greatest diagnostic yield. In our experience, when there is high clinical suspicion of RVH due to fibrodysplasia, renal arteriography can be used directly to confirm the lesion and perform a possible angioplasty. When suspicion is moderate, Doppler duplex should be used, followed by MRA or CTA, depending on the results and experience of each centre.

Treatment

The fundamental purpose of the treatment of renovascular hypertension is to control blood pressure and preserve or improve kidney function. Given the different aetiologies and courses of the vascular lesions, both diseases, fibromuscular dysplasia and atherosclerosis, should be analyzed separately.

Fibromuscular dysplasia

Blood pressure can be controlled with angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), together with thiazide diuretics. If blood pressure control is not optimal, a calcium antagonist or beta-blocker may be added [10]. The use of ACEI/ARB in patients with severe and bilateral lesions may cause haemodynamic intraglomerular alterations that deteriorate the glomerular filtration rate. This makes it necessary to monitor plasma creatinine and serum potassium.

Renal revascularization (angioplasty and surgery) is indicated in severe and refractory hypertension, and fundamentally, when there is progression of the lesions with a loss of renal function and mass. Intraluminal angioplasty is the technique of choice: the morphological results according to angiographic criteria show a beneficial grade of dilation between 83% and 100% [14–16]. The percentage of restenosis is 12% to 25%, with an evolution time of two years [14–15]. Hypertension is

controlled in 22% to 59% of these patients, improves in 22% to 74%, and is not modified in 2% to 30% of them [14–17]. Revascularization by surgery is limited to cases with aneurysms in the renal artery or angioplasty failure.

Atherosclerotic renal artery

The treatment options include antihypertensive drugs, angioplasty with endoprosthesis and revascularization surgery. However, in spite of controlling the blood pressure, atherosclerosis lesions may advance over time. In some series, progression may reach 45% to 60% in a period of less than 10 years [18]. Complete thrombosis of the renal artery has been described in 3% to 15% of cases, when the stenosis was greater than 75% [19]. Furthermore, cardiovascular disease in this population is very high, the survival rate being very limited (less than 45% in five years of evolution), especially in patients with bilateral lesions [5].

Many studies have been published with different types of treatment, non-invasive with antihypertensive drugs and revascularization, fundamentally with angioplasty, in an attempt to find differences in global and renal survival. The ASTRAL trial [20] included 731 patients randomized into two groups, medical treatment versus angioplasty, with or without endoprosthesis treatment, but the final results will not be known until the spring of 2008. Balk et al. [21] conducted a review of the literature between 1993 and 2005. They found 357 studies, only two of which were randomized. It can be deduced from the randomized and controlled studies that the cardiovascular mortality at six months was similar with both treatments. The angioplasty treatment improved the control of blood pressure when the lesion affected both renal arteries, or, in some cases, renal function. Due to the methodological differences and the different objectives established in the studies, it was not possible to draw any conclusions that would make it possible to recommend a certain therapeutic option, although initial medical treatment seems to be the most indicated.

The CORAL study [22] was designed in order to address this question. It was initiated in the year 2004 and will be completed in 2010. A total of 1,080 patients, randomized into two arms, will be enrolled:

- arm 1: medical treatment with ACEI/ARB as the first drug, adding antihypertensive agents necessary to achieve optimum control (< 135/85 mm Hg) in addition to statins and anti-aggregants;
- arm 2: angioplasty with endoprosthesis placement and optimum medical treatment.

The purpose is to contrast the effects of optimum medical therapy alone to stenting with optimum medical therapy on cardiovascular morbidity and mortality as well as renal dysfunction.

The indications to perform revascularization in atherosclerotic renal artery stenosis are shown in Table 2 [9, 10, 23–25], focusing on three different parameters: renal function, hypertension and cardiac syndrome. An intrarenal resistance index of less than 0.80 would be the marker of a good evolution. In acute renal failure secondary to aortic and renal artery thrombosis, where the kidneys have an important collateral circulation (non-functioning kidneys), surgical treatment would have a clear indication [26, 27].

Patients with established renal ischemic disease with long evolution (creatinine > 3.0 mg/dl) and decrease of renal parenchyma will not benefit from any type of revascularization.

Revascularization techniques

Angioplasty with endoprosthesis: in order to improve the efficacy of the angioplasty and decrease the incidence of restenosis in ostial lesions, it is essential to place an endoprosthesis (balloon-expandable intravascular stents) [28]. The specific complications of the technique include bruises in the puncture zones (20%), cholesterol atheroembolisms (10%), contrast-induced nephropathy and dissection of the renal and iliac arteries [28].

Surgery: This is considered to be a technique of choice (1) in those patients with pathology in the aorto-iliac arteries who will require a combined revascularization, (2) in very severe ostial lesions, and (3) in complete renal artery thrombosis.

Table 2. Indications for revascularization in atherosclerotic renal artery stenosis

Renal function
Progression of renal artery stenosis
Loss of renal mass
ACEI/ARB induced azotaemia
Hypertension
Refractory hypertension
Cardiac syndrome
Congestive heart failure
Flash pulmonary oedema

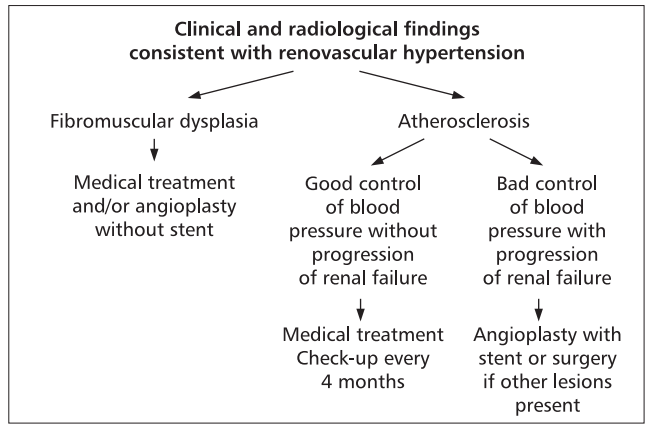

Figure 2. Algorithm for the treatment of patients with renovascular hypertension

The results published describe improvement or stabilization of the renal function in 79% to 90%, and progressive deterioration in 10% to 20%, of these cases [24, 19]. Global mortality was 4.6% and was associated with older age and symptoms of heart failure [29]. Some authors describe good results with surgical revascularization in cases of acute thrombosis of the renal artery (non-functioning kidneys) as long as some minimum criteria are fulfilled for the surgery and it is possible to place a bypass [26, 27].

Figure 2 shows the algorithm for the treatment of patients with renovascular hypertension.

In conclusion, ischemic renal disease is a complex disease with extrarenal vascular lesions that increase cardiovascular morbidity and mortality. Most of the time, renal artery lesions are due to atherosclerosis and it is recommended to begin with noninvasive techniques. Initially, medical treatment is indicated and if this does not control the hypertension and the renal function, angioplasty without stent should be used, especially in fibromuscular dysplasia. In ischemic renal disease with atherosclerotic causes, revascularization is indicated if there is a progression of the lesions with loss of renal mass and function.

The decisions should be based on individualized analysis of each patient, according to the complexity of their lesions and the experience of each centre.

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