

Atherosclerotic renovascular disease: detection and therapeutic intervention

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Abstract

Although the real prevalence of atherosclerotic renovascular disease (ARVD) as a cause of end-stage renal disease is unknown, its incidence has been increasing in the last years. The diagnosis of this pathology requires carrying out a number of functional and anatomical tests. The first approach should be to perform duplex Doppler ultrasonography, which, besides providing stenosis size and extent, allows calculation of the intrarenal resistive index as the pattern of renal parenchyma injury and the expected progression if revascularized. The most frequently used morphological techniques are magnetic resonance angiography (MRA) and computer tomography angiography (CTA). Anyway, it is necessary to perform renal arteriography regardless of the inherent risks due to contrast toxicity or atheroembolism. Different therapeutic options are reviewed, highlighting percutaneous transluminal renal angiography plus stent (PTRAS) as the first indication. Even though preliminary results were contradictory, several meta-analyses have concluded that better blood pressure control and renal function improvement are achieved with PTRAS as compared to conventional medical therapy. Surgical revascularization is preferable in patients with severe aorto-iliac pathology and renal artery ostium complete thrombosis. Every patient must be individualized and risks and benefits must be evaluated.

Key words: atherosclerotic renovascular, ischaemic nephropathy, ischaemic renal disease, renovascular disease, atherosclerotic renal artery disease, percutaneous transluminal renal angioplasty.

Introduction

Atherosclerotic renovascular disease (ARVD) can be defined as a significant reduction in glomerular filtration rate (GFR) in patients with haemodynamically significant renovascular occlusive disease (RVD) affecting the total functioning renal parenchyma.

This clinical entity can be named in different ways, and can be found in the literature as ischaemic renal disease, ischaemic nephropathy (IN), chronic renal ischaemia, azotemic RVD, atherosclerotic RVD, or renal insufficiency of renovascular hypertension [1].

Atherosclerotic renovascular disease is associated with hypertension, chronic renal insufficiency or ischaemic nephropathy, cardiovascular disease, and a twofold to fivefold increase in cardiovascular mortality.

The prevalence of ARVD has not been precisely established and different autopsy-related studies have reported an 18% prevalence in patients

aged 64-75 years, whereas it reaches 42% in patients older than 75 years old. Thus, it seems to depend on age of the population, where the higher the age the higher the prevalence of ARVD. Disease prevalence among those presenting for angiography ranged from 11 to 42%, with the greatest prevalence in those with generalized atherosclerosis, peripheral vascular disease, and aortic atherosclerotic disease [2, 3]. Chronic renal failure due to ischaemic RVD is a potentially reversible disorder. Progressive renal artery stenosis that threatens the entire renal mass, possibly resulting in renal insufficiency or end-stage renal disease (ESRD), is usually defined as significant high grade stenosis of both renal arteries or of stenosis to a single solitary kidney. It has been estimated that it may be responsible for 5 to 22% of patients with advanced renal failure who are over the age of 50 [4]. In one study, the primary diagnosis leading to ESRD in patients over 65 years of age was IN. In another series of bilateral RVD, 12% progressed to ESRD and had an average decline in GFR of 8 ml/min/year [5].

Fatica et al. reported an increasing incidence trend of ESRD caused by IN with an annualized percentage of growth for RVD-ESRD for the study period of 12.4% compared with 8.4 and 5.4% for diabetes mellitus (DM)-ESRD and all-cause ESRD, respectively [6].

Clinical findings associated with the presence of RVD are hypertension, older age, renal insufficiency, extrarenal atherosclerosis, renal artery or abdominal bruit, DM, congestive heart failure symptoms, female sex, and smoking.

An ischaemic group (GEDENI) study [7], multicentre, carried out in 20 Spanish hospitals with 156 IN patients, showed a mean age of the population of 68.7 years, with a predominance of males (78.3%). Most of them were hypertensive (97.4%), smoking (69.8%) and hypercholesterolaemic (62.9%). Isolated or associated existence of atherosclerosis in other vascular beds was present in 82% of patients, peripheral arteriopathy in more than 65%, and associated arteriopathy or ischaemic cardiomyopathy in 21.6%.

Clinical features predominant in IN are renal insufficiency and hypertension; however, in a series published by Alcazar et al., 29.5% of patients developed acute renal failure (ARF) as IN presentation: 12 patients (57%) secondary to ACE-I treatment and 28.5% due to renal artery occlusion [8]. The kidney can develop collateral circulation at the expense of the lumbar, urethral and suprarenal arteries. Therefore, the kidney may survive despite a very low filtration pressure and GFR.

In other series, when treated with ACE-I, 6 to 38% of the patients with severe RVD may develop ARF. Similarly, angiotensin II receptor antagonists (AIIRA) may produce the same

haemodynamic disorder as ACE-I and thus precipitate ARF [9, 10].

Diagnostic approach

There are several clinical characteristics that advocate a diagnosis of ARVD, and it is important to perform a complete medical history and physical examination.

Signs and symptoms which are suggestive are sudden onset of hypertension, especially in young subjects, and particularly in women; the presence of severe hypertension in males over 60 years, with signs of atherosclerosis in other vascular territories; hypertension and vascular bruit; grade III retinopathy in 25-40% of patients; elevation of serum creatinine after the administration of ACE-I or AIIRA; episodes of cardiac failure and acute pulmonary oedema; and hypertension refractory to treatment with more than antihypertensive drugs.

However, the diagnosis must rely on imaging studies to enlarge specificity to clinical clues. Ideally, the screening test should be readily available, non-invasive and non-nephrotoxic and should provide an anatomical diagnosis of IN as well as an indication of its functional significance. In addition, it must also provide information on which patients are likely to benefit from intervention [11].

The gold standard for diagnosing renal artery stenosis is renal arteriography. However, a variety of less invasive tests have been evaluated for screening purposes. False negative tests (low sensitivity) are the major concern with all non-invasive tests, since patients with a potentially correctable cause of hypertension will be missed.

Duplex Doppler ultrasonography

In experienced centres, the sensitivity and specificity of this test have been reported to be greater than 96% when both intrarenal and extrarenal arterial analyses are combined. Its most significant limitation is the localization of the renal arteries. The limitation depends on the degree of abdominal obesity, intestinal gas content, experience and patience of the observer and time spent performing the examination; thus, it has been called observer dependent.

Duplex Doppler ultrasound can enable calculation of the resistive index, which is a measure of the integrity of the small vessel circulation and of parenchymal injury. Resistive index values greater than 0.80 in the kidney contralateral to a stenosis indicate severe parenchymal disease and unlikely clinical benefit in blood pressure control and renal function recovery from revascularization. The resistive index is decreased in stenotic kidneys because of waveform dampening, and therefore lower values may not reflect preserved parenchyma

in this setting. However, a resistive index greater than 0.80 in a stenotic kidney indicates the likelihood of severe parenchymal disease and a poor clinical response to revascularization. For these reasons, duplex Doppler ultrasound is a reasonable choice as an initial screening test where expertise is available [12].

Renal scintigraphy

Currently, this technique is only used to demonstrate renal feasibility in non-functioning kidney patients.

Magnetic resonance angiography

Magnetic resonance angiography (MRA) is a test that involves the administration of gadolinium. In centres where reliable duplex Doppler testing is unavailable, gadolinium-enhanced MRA is likely to be the screening test of choice. The main problems with MRA are its tendency to overestimate the severity of the stenosis and its degree of interobserver variability. The use of gadolinium-enhanced three-dimensional MRA improves the specificity of the examination. The sensitivity and specificity of gadolinium-enhanced MRA are 97 and 93%, and for non-enhanced MRA the values are 94 and 85%, respectively [13, 14]. Combining the MRA with cardiac-gated phase contrast flow measurements can give an assessment of the haemodynamic significance of the stenosis.

Spiral computed tomographic angiography

The sensitivity of this method varies from 67 to 92%. It can be improved to 98%, with a specificity of 84%, by using maximum-intensity projections and three-dimensional techniques. The need to administer 100 to 150 ml of iodine contrast material is one of the disadvantages of this method, making it avoidable in patients with renal insufficiency. Furthermore, like MRA, computed tomographic angiography (CTA) provides only anatomical information and has not been shown to predict clinical responses to revascularization [14].

The abilities of CTA, MRA, ultrasonography, captopril scintigraphy, and the captopril test to detect ARVD were recently compared in a meta-analysis of 55 studies of patients referred for the evaluation of renovascular hypertension [15]. Spiral computed tomographic angiography and gadolinium-enhanced MRA had the highest diagnostic performance. However, both CTA and gadolinium-enhanced MRA (without phase contrast flow measurements or estimations of pressure gradients) provide only an anatomical diagnosis of atherosclerotic renal stenosis (ARAS).

Angiographic methods to state the diagnosis and ulterior management of ARVD have the concern of

radiocontrast-induced nephrotoxicity and risk of atheroembolism. The best treatment of contrast-induced renal failure is prevention. Some preventive measures include the use, if clinically possible, of scanning without radiocontrast agents, particularly in high-risk patients; the use of lower doses of contrast and avoidance of repetitive studies that are closely spaced; avoidance of volume depletion or non-steroidal anti-inflammatory drugs, both of which can increase renal vasoconstriction; the administration of intravenous saline and the antioxidant acetylcysteine; and the use of low or iso-osmolar non-ionic contrast agents [16].

The safety and lack of nephrotoxicity of gadolinium-based contrast agents in MR imaging studies for patients with normal or decreased renal function is well established. As a result, among those at risk for radiocontrast-induced nephropathy in whom vascular imaging is required, MR imaging with gadolinium is preferred to CT or conventional arteriography with iodinated contrast media. To minimize possible nephrotoxicity in MR examinations, doses of gadolinium-based contrast agents of more than 0.3 mmol/kg body weight should be avoided. The current practice of using gadolinium-based contrast media for digital subtraction angiography is limited by possible nephrotoxicity and, if the dose is below 0.3 mmol/kg for renal protection, diminished diagnostic image quality.

The use of low-dose gadolinium-based contrast agents (to 0.1 mmol/kg body weight) in patients with impaired renal function has been shown to be non-nephrotoxic, but results regarding the safety issue with a 0.2 mmol/kg body weight or higher dose are controversial in stage 3 and 4 renal failure patients [17].

Gadolinium contrast appears to be an effective agent for interventional renal angiograms. Compared to iodinated contrast, gadolinium contrast is associated with a significantly lower incidence of contrast nephropathy and early progression to end-stage renal disease in patients with pre-existing chronic kidney disease [18].

The risk of fibrosing dermopathy however remains to be established.

Differential diagnosis

Atherosclerotic renovascular disease and nephroangiosclerosis usually become visible in men aged older than 50 years with a long history of arterial hypertension and associated metabolic disorders. Renal function decline in nephroangiosclerosis is slower and frequently accompanied by mild proteinuria. Patients with systemic atherosclerosis have a high risk of developing atheroembolism with small-vessel thrombosis. Cholesterol atheroembolism is frequently precipitated by aortic manipulation,

although it can arise spontaneously. The deterioration of renal function and evidence of extrarenal lesions are manifested by digital gangrene, livedo reticularis, and the presence of hypocomplementaemia and blood and urine eosinophilia [19].

Evidence of cholesterol embolization has been found in 25 to 30% of patients who died within 6 months of cardiac catheterization or aortography. In several reports of renal artery angioplasty, cholesterol emboli were present in 0.6 to 6% of patients, with an overall incidence of 16 of 1,014 attempted dilations. In a large review of non-coronary angioplasty (4,662 renal and peripheral cases), a 4.8% incidence of embolism was found.

Angioplasty and stenting in renal atherosclerotic lesions constitute the most emboligenic part of the procedure as demonstrated both *in vivo* and *ex vivo*. Holden et al. [20] evaluated the impact on renal function using a dual therapeutic approach, aggressive balloon dilatation and stenting in combination with a distal embolic protection device. Preliminary results suggest the feasibility and safety of using distal protection devices during PTRAs and stenting to protect the distal renal parenchyma against atheroembolism and renal function deterioration.

Treatment

The aim of treatment is to protect or improve renal function. Specific management in patients with chronic ischaemic renovascular disease such as IN are medical therapy, angioplasty (usually with stent placement), and surgery.

Medical therapy

In patients with ARVD, aggressive medical management entails not just control of blood pressure but comprehensive therapy aimed at reducing the risk of other complications of systemic atherosclerosis, including stroke and myocardial infarction. Although outcome data are lacking, most investigators and clinicians have determined that lifelong antiplatelet therapy, smoking cessation and aggressive control of hyperglycaemia are indicated in patients with atherosclerosis.

At least one report has suggested that aggressive low-density lipoprotein lowering with statins leads to decreased progression of atherosclerotic ARVD [21, 22].

For blood pressure control, use of all antihypertensive classes is appropriate, and combination therapy is often necessary. Given the pathophysiology of ARVD, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are frequently required to get blood

pressure to target levels and may have unique advantages in maintaining long-term renal function in the face of concomitant medical renal disease. While contemporary data are lacking, older studies have demonstrated that a substantial number of patients with ARVD can have significant improvements in blood pressure with medical therapy alone. In these studies, acute renal failure with ACE inhibitors or ARB was rare and generally reversible with discontinuation of the agent. Although it is difficult to generalize, an increase in serum creatinine of <25% and a serum potassium of <5.5 mEq/l usually does not require discontinuation of the agent. Bilateral renal artery stenosis should not be considered an absolute contraindication to the use of ACE inhibitors and ARB.

Calcium antagonist and diuretic agents alone or in combination are also indicated in these patients.

Percutaneous transluminal renal angioplasty

With stent is an attractive option because of its relative low morbidity and mortality [23]. In severe atherosclerosis patients its efficacy decreases, especially when the ostium of the renal artery is affected. Most atheromatous renal artery stenoses are ostial, so the response to balloon dilatation may be poor and the indication for percutaneous transluminal renal angioplasty (PTRAs) must be stated taking into account these characteristics. Percutaneous transluminal renal angioplasty of ostial stenosis is only 50% successful; the incidence of restenosis ranges from 5 to 38% and a large proportion of patients suffer a decline in renal function.

Although no complete consensus exists among investigators, revascularization is indicated in patients with the following characteristics: decrease in renal artery diameter greater than 75%, progressive deterioration of renal function in individuals with renovascular disease but with satisfactory control of arterial pressure, non-reversible renal insufficiency in the presence of hypotensive drugs (excluding ACE inhibitors) as a consequence of critical stenosis, resistive index on duplex Doppler ultrasonography less than 80, and renal failure caused by aortic or unilateral or bilateral renal artery thrombosis in which the kidneys have remained viable because of collateral circulation. Van Jaarsveld et al. randomly assigned 106 patients with hypertension who had atherosclerotic renal artery stenosis and renal insufficiency to undergo PTRAs or to receive drug therapy [24]. To be included, patients also had to have a diastolic blood pressure of 95 mm Hg or higher despite treatment with two antihypertensive drugs or an increase of at least 0.2 mg per decilitre

(20 µmol/l) in the serum creatinine concentration during treatment with an ACE-I. Blood pressure, doses of antihypertensive drugs, and renal function were assessed at 3 and 12 months, and patency of the renal artery was assessed at 12 months. They concluded that for patients who have IN secondary to atherosclerotic renal artery stenosis with normal or mild impairment of renal function, primary angioplasty was not more effective than antihypertensive drugs alone for reducing blood pressure. Nevertheless, "rescue" angioplasty to control refractory hypertension was efficacious. Angiotensin-converting enzyme inhibitors renogram has little use in management of IN as it does not predict patients who will respond to therapy.

The introduction of self-expanding and balloon-expandable metallic stents (PTRAS), a treatment that might improve angioplasty results, immediate postangioplasty complications, and restenosis, has become available for atherosclerotic renal arterial stenosis. The largest review to date evaluating the efficacy of PTRAS and PTRAS was conducted by Leertouwer et al. in 2000 [25]. They included all studies dealing with PTRAS (10 articles, 644 patients) and PTRAS (14 articles, 678 patients); the population had similar characteristics: mild to moderate renal insufficiency, age 60-75. Primary outcome measures were similar (change in renal function or hypertension control, angiographic patency). They concluded that PTRAS appears to be superior technical therapy than PTRAS due to the higher initial success rate and lower restenosis rate. Stent placement was associated with a significantly lower percentage of patients with improved renal function. However, this is likely attributable to the fact that the baseline renal function was better in PTRAS studies. This meta-analysis suggests that 65 to 70% of patients do have stable or improved renal function after PTRAS/S.

Because of the lack of clear evidence that indicates the correct guidelines for IN, clinical practice is frequently based on empirical attitudes. Studies with renal function as the primary outcome are still needed and whether PTRAS improves the cardiovascular morbidity and mortality of patients is also undecided. To provide information on this subject, multicentre randomised studies are in progress.

The ASTRAL (Angioplasty and STent for Renal Artery Lesions) study started recruiting in November, and as of the end of 2006, 731 patients have been randomised to the trial [26]. Patients with a suspicious clinical presentation identified as having IN are randomly assigned to PTRAS with/without stent placement plus medical care or to medical care alone. Then there will not be restrictions on their medical treatment but ACE-I/IIIRA unless considered essential, as congestive heart failure patients. The primary

outcome is the mean slope of the reciprocal creatinine plot over time.

The CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial has been designed to test the difference in survival free of adverse cardiovascular and renal end-points in hypertensive patients; it began in 2004, with a population of about 1000 IN and the extent of 5 years [27]. The randomisation will be to renal artery stenting plus optimal medical therapy or optimal medical therapy alone. Angiotensin-converting enzyme inhibitors are not excluded from therapy due to being considered the standard of care for management of people with atherosclerotic disease. The primary end-point is a combination of cardiovascular or renal death, stroke, myocardial infarction, hospitalisation for congestive heart failure, doubling of serum creatinine and renal replacement therapy.

The RAVE (Renal Atherosclerotic Revascularization Evaluation) study is to determine the frequency of progression to the composite endpoint, death, dialysis and doubling of creatinine in patients with ARVD and an indication for revascularization, randomised to medical therapy or renal revascularization over a minimum of 6 months. The secondary objectives are to compare blood pressure and medications used in patients randomised to revascularization or medical therapy, determine the sensitivity and specificity of the resistive index values in identifying the response to renal revascularization, to determine baseline factors in people with ARVD that are associated with the indication for revascularization, and to follow patients over time for both an intent to treat and per protocol analysis of outcomes stratified by their renal resistance index finding [28].

Surgery

Surgery is still the first treatment choice in patients with IN of atherosclerotic origin. The main indication is aorto-iliac atherosclerotic involvement requiring revascularization, severe ostial stenosis and renal artery complete thrombosis. Several criteria have traditionally been used as indications for revascularization surgery: total kidney size greater than 8 cm; angiographic or scintigraphic demonstration of retrograde filling of the distal renal arterial tree from collateral vessels; patency of the distal end of the renal artery; viability of the involved kidney shown by isotopic renography; and well-preserved tubules and minimally sclerosed glomeruli in a biopsy performed before revascularization. Groups skilled in revascularization surgery have reported improvement or stabilization of renal function of 79-90%, compared to progressive decline in 10-20%. Surgery-related mortality was 4.6% and it was associated with the elderly and symptoms of congestive heart failure [29].

In conclusion, ARVD is an increasingly prevalent pathology whose early diagnosis is essential in order to avoid progression towards irreversible renal insufficiency. Once diagnosis is confirmed, an individual analysis is mandatory, evaluating the advantages and risks of renal revascularization techniques.

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