Ischemic nephropathy

Nefropatia isquêmica

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Abstract

Ischemic renal disease or ischemic nephropathy related to renovascular disease can progress rapidly and gradually to chronic renal failure. Early diagnosis and treatment are crucial for this clinical condition, because they can prevent occurrence of end-stage renal disease, with consequent necessity for renal replacement therapy. A decade ago, renovascular hypertension control was the primary objective in the management of patients with renovascular disease. Currently, the primary goal is stabilization and/or improvement of renal function, in addition to blood pressure control.

Keywords: ischemic nephropathy; atherosclerosis; renovascular hypertension.

Resumo

A doença renal isquêmica ou nefropatia isquêmica relacionada à doença renovascular pode evoluir de forma rápida e progressiva para a insuficiência renal crônica. É fundamental a identificação e o tratamento precoce desta condição clínica, prevenindo a ocorrência de doença renal em estágio terminal, com consequente necessidade de terapia de substituição renal. Há uma década, o controle da hipertensão renovascular era o objetivo primário no manejo de pacientes com doença renovascular. Atualmente, a meta está dirigida principalmente para a estabilização e a melhora da função renal, além do controle dos níveis pressóricos.

Palavras-chave: nefropatia; Isquêmica; aterosclerose; hipertensão renovascular.

Introduction

The presence of a hemodynamic significant stenosis in renal arteries can lead to two distinct and independent clinical conditions: renovascular hypertension (RH) and ischemic nephropathy (IN). The first results from a progressive stimulation of the renin–angiotensin–aldosterone system (RAAS), while the second is a consequence of the progressive reduction in the effective renal plasma flow. This flow reduction impacts the kidney excretory function leading to development of chronic renal failure (CRF).

Traditionally, the majority of the clinical studies in atherosclerotic renal artery disease or renovascular disease (RVD) focused in the physiopathology and in the management of the resulting systemic hypertension (SHT), due to the considerable clinical interest aiming a cure for secondary SHT1,2. However, in more recent years, attention has also been given to the role of the ischemia resulting from the renovascular involvement in the progressive loss of renal function. Renovascular involvement causing ischemic nephropathy (IN) contributes for the development of end-stage renal disease3-5.

IN, as a new clinical entity, refers to the presence of occlusive or anatomically advanced stenotic disease in the extraparenchymal renal artery, in a solitary kidney or in both renal arteries, with consequent global renal ischemia4,5.

It is estimated that the presence of stenosis in the renal arteries in patients with renal function deficits has been increasingly diagnosed due to the wider use of vascular...
imaging examination methods as angiography, helical computed tomography angiography (HTCA), magnetic resonance angiography (MRA) and the color flow Doppler sonography. In three studies, between 9 and 11% of the patients who performed renal angiography during cardiac catheterization for coronary angiography had a renal artery stenosis greater than 50%. Published data suggest that in the United States (US) the prevalence and annual incidence of renal disease with atherosclerotic origin in patients aged over 65 years are around 0.5 and 3.7 per 1000 patients/year, respectively.

Kalra et al. have shown a prevalence of atherosclerotic RVD of 0.5% in a random population sample of one million people with an US national health plan. Amongst these patients, around 67% showed also atherosclerotic coronary artery disease, 37% cerebrovascular disease and 56% peripheral artery disease. This study supports the idea that RVD patients have a two to four-fold higher risk of having an extra-renal atherosclerotic disease. Analyzing the subgroup of patients with diagnosed chronic renal failure, IN prevalence reaches 5.5%.

Some studies suggest that the cause of advanced renal failure is related to IN in 5 and 22% of the patients with more that 50 years of age. In this way, we should consider the possibility of ischemic nephropathy due to RVD as the cause of advanced renal failure, especially in older patients.

### Etiopathogenicity

Atherosclerotic disease is the most frequent cause of IN, being present in 60 to 97% of all lesions in the renal arteries. Other clinical conditions can also be associated with IN etiology, like the fibromuscular dysplasia (FMD), embolism, aortic and renal arteries dissection and vasculitis like Takayasu arteritis. A Caucasian origin seems also to constitute a risk factor for the developing RVD.

Renal artery atherosclerosis is predominant in male patients older than 50 years and involves mainly the proximal portion of the artery, close to its origin in the aortic artery. FMD is the most common cause of renal artery stenosis in young patients, with a great predominance in women aged between 15 and 40 years. The damage in FMD commonly occurs in the middle-distal segment of the renal artery.

The clinical progression of IN is conditioned to chronic advance of the stenotic vascular lesion. Prolonged ischemia gradually determines atrophy with loss of the renal structural integrity. Parameters indicating the minimal percentage of stenosis necessary to determine renal ischemia have not yet been established. Nevertheless it is known that lesions greater than 75% of the renal artery diameter are associated with a poorer prognosis. Curiously, some patients are asymptomatic, showing neither SHT nor signs of chronic renal ischemia, although having pronounced estenosis.

Few studies analyzed directly the structural and functional effects of the chronic reduction, in perfusion pressure on the renal tissue following a vascular stenosis. Renal ischemia leads to the release of cytokines resulting in an immune and inflammatory response. Perpetuation of this mechanism causes renal fibrosis with glomerular hyalination and size reduction, determining progressive renal atrophy.

### Clinical aspects

The diagnosis of ischemic nephropathy is frequently suggested by the medical history and by findings in physical examination. The presence of refractory SHT, uncontrollable with the use of three or more antihypertensive agents in adequate therapeutic dosages (including a diuretic), suggests a possible secondary etiology, particularly RVD. Also patients with previous adequate blood pressure control who at some point start showing a limited response to medication should be screened for possible renovascular hypertension. The same applies to patients older than 55 years who abruptly show grade II SHT (>160 × 100 mmHg). Another possible initial manifestation of IN is malignant SHT, with target organ damage leading to acute pulmonary edema (APE), hypertensive encephalopathy, congestive heart failure (CHF) and rapidly progressive renal failure.

Asymmetry in kidney size, with a difference higher than 1.5 cm between both kidneys, and an already established renal atrophy in patients with moderate to severe SHT also strongly suggests this diagnosis. It is known that a kidney smaller than 9 cm has a 75% correlation with atherosclerotic renovascular disease.

Recurrent episodes of APE or CHF accompanied of moderate to severe SHT lead to a high clinical suspicion of RVD. In a study of 55 renovascular disease patients, 23 showed recurrent episodes of pulmonary edema requiring hospitalization. This clinical picture is more often found in patients with bilateral stenosis of the renal arteries. Factors contributing to heart failure in these patients include increased afterload entailed by the SHT, inability of the hypertrophied left ventricle to relax during diastole and RAAS activation.

A higher than 30% increase of plasma creatinine after administration of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARA-II) is also a strong indicator of ischemic renal disease.
A murmur in the abdominal or dorsal region or signs of systemic atherosclerosis (coronary artery disease, peripheral arterial occlusive disease, cerebrovascular disease, aortic aneurysm, etc.) are observed in many patients.

Curiously, progression of renal artery stenosis may occur despite the adequate control of blood pressure. Several studies with arteriography or color Doppler ecography demonstrated that progression of the renal artery stenosis occurred in up to 11% of the arteries with atherosclerotic lesions in an average period of 2.6 years, reaching 30% to 60% in seven years, even with an optimized antihypertensive treatment.

Crowley et al. described that patients with a stenosis higher than 75% in one or in both renal arteries had a significant increase of serum creatinine (on average by 1.6mg/dL) when compared to normal individuals. These authors also observed that both treatment with percutaneous transluminal angioplasty (PTA) or surgery were not able to bring a significant improvement to final outcome.

Previous studies show that progression to total occlusion occurred in around 10% to 15% of the stenotic arteries, especially on those showing a lumen narrowing higher than 75%.

Diagnosis

According to Textor, there is no noninvasive test alone that is sensitive enough to diagnose or exclude the presence of bilateral RVD.

Creatinine clearance (CC) is gaining an increasing importance as marker of kidney disease and as predictor of renal function after revascularization procedures. CC is better than creatinine level alone to estimate kidney function, due to a reduced influence of age, muscle mass and patient nutrition level. A study by Cianci et al. demonstrated a correlation between CC and the prognosis of patients after angioplasty.

The American College of Cardiology recommends that imaging examinations should be done only in patients presenting with the previously described signs and symptoms suggestive of RVD, in which the probability of a surgical intervention is high.

In face of an IN suspicion, renal ultrasonography should be firstly requested. The exam properly assesses kidney size and its ecographic characteristics. Nevertheless, it should be noted that its accuracy is low, as patients whom stenosis of both renal arteries can show symmetric kidneys with apparently normal size, while kidney asymmetry can also occur in cases of unilateral parenchymal disease from other ethiology.

Color Doppler renal sonography is able to evaluate blood flow in renal arteries with sensitivity ranging 95 to 99% and specificity of 97%. The capacity of this technique in detecting stenosis in renal arteries was described in a meta-analysis of 88 studies that evaluated 9,974 arteries in 8,147 patients. The peak systolic velocity showed greater accuracy than the determination of the renal-aortic ratio and the acceleration index, with a sensitivity of 85% and a specificity of 92%. It is specially indicated in patients with an impairment of renal function (creatinine higher than 2 mg/dL). Other indication is the follow-up after renal revascularization procedures by PTA or surgery. However, this test is operator dependent and requires time for its correct accomplishment.

MRA is considered a first-line test screening for RVD, with a sensitivity of 96% and specificity of 94% when compared with hTCA. MRA is considered as the noninvasive method of choice for diagnosing renal artery stenosis in patients with normal renal function. However, it should be noticed that administration of gadolinium during MRA in patients with moderate to severe renal failure (particularly in patients on dialysis) has been associated to a severe disease called nephrogenic systemic sclerosis. Nephrogenic systemic sclerosis or fibrosis is relatively rare and affects mainly patients with renal failure, with skin and connective tissue fibrosis throughout the body. The cutaneous lesions are usually symmetric. Due to the possibility of inducing this severe syndrome, it is recommended that administration of gadolinium should be avoided in patients with glomerular filtration rate less than 30 mL/min.

Two studies have shown that hTCA has a sensitivity of 98% and a specificity of 94%. It is a great option as initial screening test, but with the inconvenience of requiring a big volume of iodinated contrast media, around 150 mL.

Renal arteriography is the gold standard test for the diagnosis of stenosis in renal arteries, although it does not assess the functional consequences of the stenotic lesions. Being invasive, this procedure presents several complications. Among these are cholesterol embolism, hematoma at the puncture site, pseudoaneurysm formation, arterial thrombosis and iodinated contrast media induced acute renal failure.

Currently, due to these complications, arteriography is indicated only for cases with a diagnostic suspicion established by the use of a noninvasive method (color flow Doppler sonography and captopril renal scintigraphy), in cases where it is not possible to perform hTCA and MRA.
and in all cases in which is intended to perform renal revascularization procedures by PTA or surgery. Renal scintigraphy before and after captopril administration performed in patients with high probability of RVD has sensitivity and specificity higher than 90%. The test is considered positive when a decrease higher than 40% is observed in the glomerular filtration rate in solitary kidney, or there is a delayed peak in glomerular filtration rate to more than 10 to 11 minutes, considering that the normal would be 3 to 6 minutes. These criteria should be evaluated separately in each kidney to make possible the detection of bilateral RVD. The technique is very useful in patients showing no renal failure, besides that it depends just a little on the examiner and does not carry any risk of contrast media nephrotoxicity. However, renal scintigraphy is not considered a first choice method for renal ischemic disease screening by the American College of Cardiology.

**Treatment**

Total and bilateral occlusion of renal arteries does not necessarily determine an irreversible ischemic parenchymal lesion, as the renal viability can be maintained for long periods through collateral blood circulation coming from ureter, lumbar, adrenal and capsular blood vessels. Commonly a renal artery stenosis is considered hemodynamically significant when it causes a decrease in the blood flow and pressure (called a pressure gradient), which is observed with lesions showing more than 70 to 80% of luminal stenosis. The clinical importance of ischemic nephropathy lies in the fact that the determined renal failure can be prevented or reversed if the correct diagnosis and treatment are applied early during its progression while viable renal tissue is still present. Reversion of anuria and renal function recovery have been described in specific cases after revascularization of totally occluded arteries, in which the response to treatment occurred some days or even weeks after the occlusion. In these cases, renal viability, in detriment of renal function, is maintained through subfiltration perfusion pressure.

Currently there are two therapeutic alternatives for RH management: (1) isolated expectant pharmacotherapy; (2) interventional therapy with renal revascularization (PTA, with or without stenting, and surgery). A systematic review published in 2006 on RVD management concluded that there is no solid evidence about which would be the best therapy for this condition. Patients with atherosclerosis should be aggressively treated aiming to stop disease progression and to prevent secondary cardiovascular events.

In this way, treatment includes the use of antiplatelets drugs, statins, blood pressure control, smoking cessation and a tight glycemic control in patients with diabetes mellitus. Calcium antagonists, like anlodipine, are first choice drugs used in the pharmacotherapy of IN, because they increase glomerular blood flow via a dilator effect in the afferent arteriole. These drugs are great options and can be used in association with ACE inhibitors, ARA-II, diuretics and beta-blockers. Pharmacotherapy with antihypertensive drugs, in particular ACE inhibitors or ARA-II, can effectively control blood pressure in many patients with uni- or bilateral renal stenosis. However, these drugs should be carefully used when stenosis is greater than 70% bilaterally or in solitary kidney. Not rarely, SHT is refractory to therapy and such patients become candidates to revascularization.

The encouraging experiences with surgery and PTA, although with heterogeneous individual responses, justify a more aggressive approach in this disease. Revascularization of an ischemic kidney could, theoretically, result in functional recovery and determine the dramatic suspension of dialysis. In this context, IN could constitute a potentially treatable cause of renal failure.

Due to the good results, conventional PTA is the chosen strategy for the treatment of RH caused by FMD in young patients. It shows restenosis in approximately 10% of the patients. In cases of renal atherosclerosis with RH and a stenosis greater than 75%, renal revascularization is indicated in the following situations: SHT uncontrolled by pharmacotherapy (in optimized dosages); rapidly progressing SHT; recently started CHF; recurrent and hypertensive APE and recent deterioration of renal function.

However, revascularization is only indicated when signs suggesting renal viability are observed, more notably renal diameter greater than 8 cm and a scintigraphic uptake above 15% when compared with the total uptake. A renal resistance index in the color flow Doppler sonography over 0.8 is a predictor of a poor response to therapy. Lesions with less than 50% of luminal reduction do not have indication for revascularization because they do not have hemodynamic consequences.

Success rate of angioplasty with stenting (the cure or improvement of SHT) is between 65 to 80% with the last studies reporting restenosis around 11% to 17%. Surgical techniques used for renal revascularization are bypass and endarterectomy. Due to a high mortality rate (around 10%) surgery is currently reserved only for complex lesions without possible treatment via PTA with stenting and for cases showing associated lesions in the aorta.
Prognosis

Renal ischemic disease with an atherosclerotic origin has a rapid clinical progression when compared with other nephropathies also with a progressive character. The rapid clinical progression is observed in the stenotic lesion itself as well as in the consequent alterations in renal structure and function.16,24,35,33,35

Prognosis of IN patients on chronic dialysis is very poor when compared with other forms of renal failure, as in terms of quality of life as in terms of longevity with mortality rates situated between 20 and 30% per year16.

Conclusion

Atrophy of tissues and organs subjected to chronic ischemia is the result of adaptive modifications aiming to balance oxygen supply and demand. However its limits, meaning until which point atrophy is beneficial, protective and reversible, are not established.

Renal artery stenosis greater than 70% generally relates with ischemic symptoms, leading to secondary SHT, many times expressed through malignant SHT. Renal artery stenosis should also be considered in patients presenting no improvement of pressure levels with the use of three or more antihypertensive drugs, including a diuretic, or presenting worsening renal function while using ACE inhibitors.

When facing cases with clinical suspicion of ischemic nephropathy, it is suggested to use middle to highly accurate noninvasive tests, as hTCA, MRA or color flow Doppler sonography. The gold standard exam for the detection of renal atherosclerosis is the renal arteriography, which is indicated in cases with uncertain diagnosis or when there is indication for renal revascularization.

Patients with atherosclerotic RVD should be aggressively treated for prevention of secondary cardiovascular disease. Treatment should include the use of antplatelets agents, statins, blood pressure and glycemic control and smoking cessation. In FMD patients, it is common the complete cure of SHT after PTA.

For SHT management, association between calcium antagonists and ACE inhibitors or ARA-II is usually beneficial, and a diuretic agent can be added to achieve the desired pressure levels. Patients with SHT refractory to adequate pharmacotherapy or with severe and clinically relevant stenosis in the renal artery should be subjected to revascularization, being TPA the first choice. However, several studies2,3,6,16,24,35,33,35 have shown divergent results concerning the RVD treatment, the stenosis grade that should be considered significant, and the use of interventional treatment aiming to prevent further progression to renal failure.

In this context, in which certainly histopathological modifications produced by IN are also included, several crucial questions remain unanswered and require further investigation: (1) From which level a reduction on blood flow starts impacting renal function? (2) IN is simply renal cells death due to the lack of oxygen and nutrients, or there exist more complex renal mechanisms of cellular lesion, adaptation and eventual repair when cells are subjected to chronic ischemia? (3) Are there histological markers on which the reversibility of the clinical picture with renal revascularization (TPA or surgery) depends? To elucidate these questions, more studies are necessary assessing this important cause of secondary SHT. It is also necessary a high suspicion index for this disease and a knowledge of its possible manifestations and consequences.

References


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