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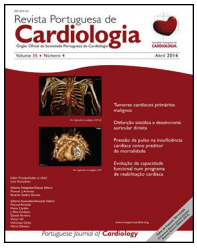

EDITORIAL COMMENT

Renovascular hypertension: The current approach

Hipertensão renovascular – abordagem atual

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Renovascular hypertension is the main cause of secondary hypertension, affecting 0.5-5% of the population, and as many as 30% of cases in selected populations.[1–4]

Strictly speaking, renovascular disease is a more correct term than renovascular hypertension, as it refers to an obstructive condition of the renal arteries that, although it may be associated with hypertension, also causes progressive ischemic kidney disease.[5]

Although clinical trials[6–9] show that invasive intervention to treat renal artery stenosis does not benefit most patients, there is evidence in the literature that intervention can benefit well-selected patient groups in terms of better blood pressure control and reductions in progression of renal dysfunction and episodes of acute pulmonary edema in bilateral renal artery stenosis, helping to stabilize or improve these patients' cardiovascular prognosis.

In their study published in this issue of the *Journal*,[10] Pedro et al. analyze the experience of a Portuguese working group in the endovascular treatment of selected patients with severe atherosclerotic obstructive lesions of the renal arteries, characterizing early and late results, and aiming to find indicators to better select and treat candidates for endovascular intervention.

Harry Goldblatt demonstrated in 1934 that renal artery stenosis caused hypertension and was also associated with chronic kidney disease, due to renal ischemia. This hypertension is the clinical consequence of activation of the renin-angiotensin-aldosterone system (RAAS). Renal artery stenosis gives rise to a series of stimuli that lead to the release of renin and the secondary elevation of blood pressure. This hyperreninemic condition promotes the conversion of angiotensin I to II, causing severe renal artery constriction and aldosterone release. The sequence of events that occur at this point depends on whether there is a contralateral kidney and its function (one-clip, one kidney hypertension and two-clip, two kidney hypertension).[1–3,5]

When there are two functioning kidneys, aldosterone-mediated sodium and water retention is appropriately managed by the contralateral kidney, and thus angiotensin II-mediated hypertension predominates. In contrast, if there is only a single kidney without sufficient salt and water excretion capacity, a volume overload component is added, which triggers hypertension.

A number of pressor mechanisms influence the clinical situation in various ways, including activation of the RAAS, recruitment of oxidative stress pathways, and activation of the sympathetic adrenergic system with intrarenal and systemic repercussions.[11,12] Human studies indicate that the development of this process requires a gradient across the atherosclerotic plaque, such as a distal pressure drop of at least 10-20% below aortic pressure. This pressure difference corresponds to a peak translesional systolic gradient of 15-25 mmHg and develops only when vessel occlusion approaches 70-80%. This indicates that vascular injury, which does not cause this gradient, is unlikely to be involved in renovascular hypertension and therefore to benefit from revascularization procedures.

The kidney as a filtering organ is relatively overperfused in relation to its metabolic needs. It thus has considerable adaptability, allowing blood flow and filtration to drop without jeopardizing its viability. A reduction in renal blood flow sufficient to reduce kidney size and produce renin may develop while oxygenation of cortical and medullary tissue are still maintained. This implies that renovascular hypertension does not depend solely on ischemia itself.[12,13]

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Alterations in post-stenotic renal flow are thought to be implicated in the mechanisms of interstitial fibrosis. Note that this rarely happens in fibromuscular dysplasia, which implies that the atherosclerotic environment induces fibrosis as a result of post-stenotic remodeling mechanisms.

Distal vascular rarefaction occurs within the post-stenotic kidney, with numerous pathways leading to upregulation of cytokines and inflammatory mediators including tumor necrosis factor-beta. Over time arteriolar rarefaction develops, associated with fibrogenesis and loss of tissue viability leading to deterioration of renal function.[5,12] Renovascular disease has been associated with various clinical conditions. Renal artery stenosis is often an incidental finding on other tests and has little impact regardless of renal perfusion, blood pressure or glomerular filtration rate (GFR). Noninvasive examinations overestimate the severity of vascular lesions. On angiography, many lesions are commonly below the threshold for endovascular intervention. In the Stent Placement in Patients with Atherosclerotic Renal artery stenosis (STAR) trial,[14] 28% of patients did not undergo intervention. When renal perfusion is reduced there may be an increase in blood pressure, accelerating pre-existing primary hypertension. Clinical manifestations often appear in treated patients; a rapid rise in blood pressure can cause target organ damage such as stroke, or when associated with reduced global kidney perfusion and increased tubular sodium resorption can lead to rapid development of circulatory congestion, termed flash pulmonary edema. Sodium retention in patients with left ventricular dysfunction leads to refractory congestive heart failure, particularly when there is bilateral renal artery stenosis or when there is only a single functioning kidney and if they already have chronic kidney disease.

The treatment decision depends on whether clinical manifestations can be controlled with medical therapy. If blood pressure is controlled and renal and cardiac function remain stable, there is probably no advantage in proceeding to invasive methods that may induce further comorbidities and associated adverse effects. If it is decided to proceed to further investigation, existing decision-making algorithms should be followed, taking into account locally available examinations, knowledge of the various techniques and the expertise to decide on the type of revascularization, and whether the patient has estimated GFR <30 ml/min/1.73 m^2.[1–4]

At present the approach tends to be more conservative than at the beginning of this century. Observational studies conducted in the 2000s and the CHORAL and ASTRAL prospective clinical trials[6–8] showed that it is important to calculate the benefits and risks for each patient, since mortality associated with surgical revascularization is up to 9% and endovascular revascularization has modest success in most patients and should thus be reserved for those who are most likely to benefit clinically. In any case, the investigation will aim to determine whether the stenosis is unilateral or bilateral, its location, and whether it is hemodynamically functional.[10,15] Its severity and accessibility and functional kidney status should also be determined. Given all this information, the decision whether to revascularize will depend on whether the clinical setting can be attributed to the lesions found and whether treatment is likely to restore the patency of the vessel. It is usually difficult to satisfy all these objectives with a single examination. Most of the tests proposed have inconclusive results when applied in several studies, with factors related to technical execution, observer expertise, the patient's condition as an effect of therapies performed, and renal function at the time of assessment all affecting the results. There is thus considerable room for improvement in diagnostic methods in these cases, and better tools are required to assess the clinical impact of renal artery stenosis.[1–3]

As seen above, diagnostic investigation nowadays depends on the response to conservative medical therapy.[5,16] In patients with uncontrolled hypertension, medical therapy is the first step. In patients with accelerated or malignant hypertension, blood pressure control should be achieved prior to any diagnostic exams. In general, hypertension control initially relies on RAAS blockers. Data from Canadian and Italian registries[3,5] show that there are survival advantages in patients who tolerate angiotensin-converting enzyme inhibition or angiotensin receptor blockers. The HOPE[17] and PEACE[18] trials suggest that the greatest benefit is for patients with renal impairment. In these studies, however, there was a high prevalence of deterioration of renal function and hyperkalemia in patients with worse atherosclerotic disease affecting afferent arterioles, which contraindicates these drugs. The creatinine rise in these patients shows that renal flow is dependent on angiotensin levels. In such cases other classes of drugs will need to be used, and kidney function reverts after stopping RAAS blockers. The CORAL trial researchers[8] argue that cardiovascular risk is amplified by neurohormonal activation, so the use of these drugs should be encouraged. Equally important is the focus on controlling other factors that promote atherosclerotic disease, because the prognosis of these patients depends primarily on extrarenal complications such as stroke, coronary events and peripheral vascular disease.[1–3]

When, then, should revascularization be performed? The rationale of this therapy is that restoring renal flow and removing the pressor effect of stenosis would achieve a cure for this form of hypertension.

In cases of renal artery dysplasia in young populations, as long as there is no aneurysm, angioplasty appears to be a low-risk approach in women, since they cannot take RAAS blockers during pregnancy. Series show that although the cure rate is less than 30%, angioplasty reduces the need to increase therapy by 50% and the degree of restenosis by 11-23%.[5,19]

In atherosclerotic disease intervention rarely lowers hypertension to normal levels, and maintenance of antihypertensive therapy is required. Establishing renal blood flow offers the potential for recovery of renal function and improved blood pressure control.

Various studies have proved unable to demonstrate benefits of revascularization, and this approach is expensive and not risk-free. Populations are heterogeneous, including elderly patients with various types of atherosclerotic target organ damage, and the STAR[14] and ASTRAL[6,7] trials had difficulty in determining the degree of stenosis and in defining critical stenosis.

However, endovascular revascularization has also had positive effects, with a drastic reduction in the risk associated with the technique, the rate of moderate complications

currently at <10%. Restenosis remains high and develops in 10-15% of patients. If abdominal aortic atherosclerosis has resulted in atherosclerotic lesions, both surgical and endovascular revascularization carry the risk of atheroembolism. When this occurs locally as a consequence of the guidewire, the rate is low (about 1-4%), but when it has systemic repercussions the consequences can be devastating. Risk factors for this situation are large atherosclerotic plaques, aneurysms, uncontrolled hypertension, and direct manipulation of the renal artery. The use of embolic protection devices at the time of the procedure does not provide the expected benefit as embolization may continue for several days after the procedure.[5]

Recovery of renal flow is not directly related to the restoration of renal microcirculation.[19] It all depends on inflammatory and fibrogenic mechanisms, which are triggered at different times. Experimental studies show that there may be migration of both local and systemic pluripotent cells that may support the regeneration of functional cells to repair damaged tubules and glomeruli.[5]

To conclude, from a clinical point of view, a clear distinction should be made between renovascular atherosclerotic disease and hypertension caused by renal artery stenosis through activation of the RAAS. The role of hypertension specialists and nephrologists is to identify the subgroups of patients at risk of progressive ischemic nephropathy and end-organ damage at a time when they may still benefit from revascularization. However, with very few exceptions, medical therapy with antihypertensive drugs and statins remains the cornerstone for the management of patients with atherosclerotic renal artery stenosis and hypertension.

The current guidelines recommend revascularization only when hypertension control cannot be achieved, if renal function is declining, or in cases of flash pulmonary edema. Otherwise, intensive medical therapy including antihypertensive drugs combined with lipid and glucose control and antiplatelet therapy is appropriate and effective in renovascular disease management.

It should be noted that previous large studies did not enroll populations at high risk of renovascular hypertension who would be more likely to benefit from revascularization procedures. Thus, randomized controlled clinical trials designed to identify these patients and clarify this issue are needed.

Pedro et al.[10] assess the endovascular approach in atherosclerotic renal artery stenosis and show that it has beneficial effects on blood pressure and renal function in this group of patients, and is a safe technique associated with a high rate of technical success and few complications. Their study thus contributes to the search for indicators and improved methods in the procedures performed, in an attempt to identify the best strategies for treating these patients, who are usually excluded from large clinical trials.

Conflicts of interest

The author has no conflicts of interest to declare.

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