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GUIDELINES

Clinical Management of Renovascular Hypertension

Practical recommendations from the Italian Society of Hypertension (SIIA)

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Abstract Renovascular hypertension (RVH) is one of the most frequent forms of secondary hypertension but this diagnosis is often missed because of insufficient care taken in collecting patient's history and clinical signs. Herein we summarize the clinical, instrumental and laboratory clues which should raise the suspicion of RVH. In addition we briefly discuss the available evidence in favour and against the revascularization therapy and, at the light of the uncertain benefit of this procedure, the alternative approach with pharmacological treatment.

Keywords Renovascular hypertension · Renal artery stenosis · Renal revascularization · Renin determination

1 Introduction

Hypertension is a major modifiable risk factor, which significantly and independently increases the risk of developing major cardiovascular (CV) complications, mostly myocardial infarction. On the other hand, an effective treatment of hypertension substantially reduces the risk of developing such complications. However, the control of blood pressure (BP) remains largely unsatisfactory in most Western countries, including Italy.

Recent analysis of data collected at the European level on BP control rate have demonstrated, in fact, that only 20–30 % of treated hypertensive patients achieve the recommended BP goals [1–4]. For example, in our Country, results from observational studies conducted between 1995 and 2005 demonstrated that in more than 52,000 of treated hypertensive patients, about 39 % had grade 1 hypertension (140–159/90–99 mmHg) and about 32 % had grade 2 hypertension (160–179/100–109 mmHg) [5]. A recent update of this analysis, which took into account studies conducted in Italy from 2005 to 2011 and included approximately 160,000 patients with hypertension mainly followed in the context of General Practitioners, reported that only 57 % of patients with hypertension were adequately treated, among which only 37 % achieve effective BP control under treatment [6]. These results confirm that BP control amongst the hypertensive population is still largely unsatisfactory in Italy.

Since hypertension is an ideal identifiable target to reduce global cardiovascular risk, it is clear that effective strategies, aimed at improving high BP control in the general population of hypertensive patients, represent a fundamental step of any preventive strategy in our Country, as well as in Western and Developing Countries, with subsequent beneficial effects for the National Health System.

Based on these considerations, the Italian Society of Hypertension (SIIA) aims to generate, circulate and share a number of interventions to improve BP control in Italy. Among the various initiatives, which include integrated and concerted actions with General Practitioners, the implementation of hypertension awareness in the general population through a more extensive use of new media and social networks, a larger use of home BP measurements, a survey aimed at identifying all clinical and excellence centers for hypertension diagnosis and treatment distributed throughout the whole national territory, there is also the production of consensus documents [7, 8] and practical

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recommendations covering specific and controversial issues of the clinical management of hypertension, that can complement those presented by the main international societies [9–12]. As such, these practical recommendations are targeting both the general practitioner and the specialist who play an active role in the clinical management of patients with arterial hypertension.

In the present document we aimed at summarizing the essential information practitioners should know about diagnosis and therapy of the commonest forms of secondary hypertension providing them with an easy and rapid consultation tool which may help in generating the suspicion which can lead to a brilliant diagnosis and, above all, to a great benefit for patients.

2 Definition

According to conventional vision, secondary forms of hypertension are quite rare and their relative low prevalence is often an alibi to justify the physician's scarce propensity to search them. This is a mistake firstly because secondary forms are far from being rare and, secondly, because patients with these disorders can be treated in a much more specific and efficient way which, in some occasions, allows a complete cure of hypertension. Moreover, in front of the initial cost for reaching the diagnosis, the identification of secondary forms of hypertension is associated with the reduction of the pharmacological burden with a life-long saving of economical resources.

Unfortunately, secondary hypertensions can be only suspected on a clinical base and never diagnosed with certainty (with the exception of aortic coarctation, where the presence of an interscapular bruit in a young hypertensive patient is typical of this disease). Moreover, the diagnostic suspect of secondary hypertension can arise only from a careful and detailed collection of patient's history and an equally accurate physical examination, diagnostic tools that, even nowadays, are more effective than any instrumental or laboratory test, but hardly compatible with the daily busy schedule of general practitioners.

3 Epidemiology

Renal artery stenosis (RAS) is the anatomical substrate of renovascular hypertension (RVH). However, the two terms are not equivalent because not always RAS is haemodynamically significant and responsible for the increase in blood pressure. As a consequence of ageing of general population and of the large spreading of imaging techniques, RAS is diagnosed more often than in the past. In an echographic study carried out in hypertensive patients with a mean age of 77 years, the prevalence of RAS >60 % was 6.8 % [13], but it may be higher in clinically pre-selected patients. For instance, in the Italian Study Group for Renovascular Hypertension (GIRV) we found that 243 (52 %) out of 459 hospitalized patients undergoing a renal arteriography for suspected RVH actually had RAS, 178 of them (38.8 %) of the atherosclerotic type (AS-RAS) and 65 (14 %) of the fibromuscular one (FM-RAS) [14]. However, in the GIRV Study, on the basis of pressure response to renal angioplasty (RA), the prevalence of RVH was 6.4 % in patients with AS-RAS and 31.3 % in those with FM-RAS. Similar data are reported in literature [15].

4 Pathogenesis

In 80–85 % of cases RAS is of the atherosclerotic type and involves the proximal third of the renal artery, not infrequently bilaterally. The remaining 15–20 % is represented by fibromuscular RAS, usually found in young women with congenital dysplasia of the vascular wall. In the early phases of RVH baroreceptor activation in the ischemic kidney increases renin secretion, causing blood pressure elevation. Thereafter, the renin–angiotensin–aldosterone system (RAAS) activation is progressively attenuated and plasma renin levels may return within the normal range but still remaining inappropriately high for blood pressure levels. It is likely that in RVH the cardiotoxic effects elicited by the activation of the RAAS and of additional humoral factors (cathecholamines, endothelin, cytokynes) contribute to the adverse consequences of blood pressure increase, exposing patients to a global cardiovascular risk particularly high.

5 Diagnosis

5.1 Clinical Signs

Various clinical signs can suggest RVH but none has sensitivity and specificity high enough to make the diagnosis certain. For example, in the GIRV Study resistant hypertension was present in 50–60 % of cases but this condition is also frequent in patients with essential hypertension. Other signs like renal asymmetry and hypokalemia are characterized by good specificity but poor sensitivity, in that they are present in only 10–20 % of cases of RVH. However, the predictive value of clinical signs increases by 2–3 folds when two or more of them coexist.

5.2 Instrumental Diagnosis

In our experience renal ultrasound with echoDoppler velocimetric study of the renal arteries is the preferable

screening test for the diagnosis of RAS. In particular, the so called "distal" velocimetric indices (acceleration and acceleration time), evaluating flow velocity at the renal hilum and in the interlobar arteries, are highly predictive of hemodynamically significant RAS [16]. Echo-Doppler velocimetry is feasible in the large majority of patients and, in expert hands, has a sensitivity and specificity (90 %) comparable to computerized angio-tomography (angio-TC) and angio-Magnetic Resonance (angio-RM). These two techniques provide direct imaging of the RAS but require the infusion of contrast medium whose nephrotoxicity can be particularly harmful in patients with moderate-to-severe renal insufficiency. Moreover, angio-RM tends to overestimate the degree of stenosis, especially in distal and accessory arteries. Renal scintigraphy doesn't provide morphological data but it allows to evaluate glomerular filtration rate (GFR) and renal plasma flow (RPF) of single kidney. Diagnostic accuracy of this test can be ameliorated with the administration of an angiotensin converting enzyme inhibitor (captopril) but false negative examinations can occur when RAS is bilateral. Renal angiography remains the gold standard but it is an invasive investigation and it should be limited to patients with a high likelihood of RAS and possible candidate for renal angioplasty.

5.3 Laboratory Diagnosis

Renin determination in peripheral blood is still a useful tool to evaluate the hemodynamical relevance of the RAS. However, the diffusion of this test has been hampered both by methodological problems related to the poor reproducibility of plasma renin activity (PRA) determination among laboratories and to the difficulties in interpreting these results related to the pharmacological interference of most antihypertensive drugs on RAAS activity. Recently new methods for the direct determination of plasma renin concentration (PRC) with monoclonal antibodies have been developed. This technique, being faster and simpler than PRA, may allow a wider application of renin determination for the diagnosis of RVH [17]. Various alternative parameters have been proposed for the evaluation of the hemodynamic relevance of RAS (BNP, calculation of trans-stenotic gradient, ultrasound resistive indices) but none of them has reached enough consensus to be exploited for clinical use.

6 Therapy

6.1 Revascularization Therapy

For patients with true RVH, especially if due to fibromuscular RAS, revascularization remains the therapy of choice. Gold standard is represented by renal angioplasty (RA) combined, in AS-RAS, with stent placement. Surgical revascularization has been progressively replaced by RA, which is less invasive, repeatable and characterized by lower mortality [18]. This procedure is technically successful in 98 % of cases with an incidence of restenosis of 15 %, an event that can be significantly prevented by the administration of antiplatelet agents for at least 6 months. For AS-RAS, there is no solid scientific evidence in favour of the benefits of RA in comparison with medical therapy. In three comparative randomized studies available up to a few years ago there was no demonstration of significant differences neither for blood pressure control nor for rescuing of renal function [15]. Yet, these negative findings cannot be generalized for the relatively small number of patients enrolled and for the high percentage of patients initially randomized to medical treatment and successively treated with RA. More recently, a randomized study conducted on a large cohort of patients confirmed the substantial equivalence of benefit deriving from RA and medical therapy [19]. However, also this study is heavily biased by relevant methodological limitations and, more importantly, by the fact that numerous patients randomized to RA had RAS <50 % and, consequently, were unlikely to have favourable effects on blood pressure and renal function. While waiting for the results of further studies the selection of patients candidate for RA still rests on clinical judgment, Strong indications for RA are the progressive decline in GFR, the acute GFR reduction as a consequence on treatment with RAAS inhibitors, RAS in patients with single kidney, or finally resistant hypertension and recurrent flash pulmonary oedema in bilateral RAS.

6.2 Medical Therapy

Due to the uncertainty about the benefits of RA, medical therapy is advisable in patients with RAS <50–60 % or when blood pressure is under control with a moderate pharmacological burden. RAAS antagonists are particularly effective in reducing blood pressure but they can reduce GFR in the stenotic kidney. This can have little effect on indices of overall renal function because of the compensatory role of the contralateral kidney, but it can cause a progressive deterioration of renal function in the stenotic kidney leading to atrophy. When using a RAAS antagonist in patients with RAS it is advisable to withdraw this therapy in case of increments in serum creatinine values of more than 30 % or for potassium above 5.5 mEq/l. Modifications of this magnitude, if confirmed, should always bring about the suspicion of a critical RAS. Also beta blockers can achieve an adequate blood pressure control, inhibiting sympatho-mediated renin secretion without significantly influencing RPF. Calcium antagonists

are advisable for their known anti-hypertensive and anti-atherogenetic efficacy. Diuretic shouldn't be considered as first line drugs because they further stimulate the activity of RAAS, unless a severe renal insufficiency coexist. On the basis of the elevated cardiovascular risk profile of RVH patients, the association of antiplatelet agents and statins to antihypertensive treatment is generally recommended.

7 Conclusions

Practitioners should know that renovascular hypertension is more frequent than previously suspected. Careful collection of patient's history and objective signs is essential before moving to sophisticated diagnostic procedure. Once correctly diagnosed renovascular hypertension can be advantageously treated with revascularization of stenotic renal artery aiming to improve blood pressure control and to prevent inadvertent loss of renal function.

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