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CONTROL OF HYPERTENSION IN PATIENTS WITH PERIPHERAL ARTERY DISEASE

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Intermittent claudication of the lower limbs is the most common clinical manifestation of peripheral artery disease (PAD). Intermittent claudication often devalues the quality of life of those suffering from it. However, much less widely known is the fact that it also carries a very high risk for cardiovascular morbidity and mortality. Conversely, hypertension is also a risk factor for vascular disorders, including PAD. There is no consensus yet on the specific treatment of hypertension in PAD because of the limited number of controlled studies on antihypertensive therapy in such a specific PAD population [1]. The approach to this clinical problem will be outlined in this short review.

Epidemiology

The prevalence of intermittent claudication in males is approximately 1.5% in those below 50 years of age and reaches 4% to 5% in those above 50. In females the prevalence is lower in those below 50 but, contrary to common belief, it is as high as in males of over 60 [2]. The prevalence of asymptomatic PAD is approximately twice that of claudication, as at least half to two thirds of individuals with PAD are asymptomatic or have atypical limb exertional symptoms.

The clinical problem

The clinical syndrome of intermittent claudication has taken on a new dimension as it has become clear that, beside the symptoms of aching pain in the legs during exercise, these patients are carrying an increased risk of cardiovascular morbidity and mortality. PAD has therefore become an important marker of systemic atherosclerosis [3].

The most potent risk factors for PAD comprise age, smoking and obesity. There is a striking association between diabetes mellitus and atherosclerotic vascular disease. Additional risk factors are hyperlipidaemia, hypertension and elevated plasma homocysteine [4–5].

Hypertension is associated with the development of atherosclerosis, particularly in the coronary and cerebral circulation, as well as with a twofold to threefold increase in the risk of claudication [4–5]. Conversely, PAD patients are faced with a significantly increased prevalence of hypertension.

These data show that PAD and hypertension are very often linked to each other, which not only greatly increases total CV risk but also represents a new challenge for treating both conditions in the same patient.

Treatment of hypertension and of intermittent claudication

Treatment should focus on improving the local symptoms in the legs, on controlling blood pressure and on decreasing total CV risk. For local symptoms the general rules concerning lifestyle adaptation remain the same: regular exercise and cessation of smoking [6]. The two most accepted drugs for increasing claudication distance are naftidrofuryl [7], which also improves the quality of life [8], and cilostazol, a phosphodiesterase inhibitor, more often used in the USA and Japan [9].

There is no convincing evidence of any superiority of one hypertensive drug over another in improving claudication distance. Neither is there any convincing proof that better blood pressure control can be obtained with one specific antihypertensive drug compared to another. Slightly better results are obtained by ACE inhibitors; in some studies an increase in muscle blood flow has been shown; ACE inhibition has also been shown to be accompanied by a limited increase in walking distance [1, 10]. Contrary to common belief, there is no deleterious effect of beta-blocking agents on walking distance [11, 12]. An interesting feature has also arisen from studies with moxonidine, a newer drug in the class of central antihypertensive drugs; this drug has been shown to increase insulin sensitivity [13], an appealing factor in view of the fact that many PAD patients have an increased insulin resistance. This could be a very helpful application in patients with metabolic syndrome, as have many PAD patients.

The level to which blood pressure should be decreased in PAD patients with hypertension has not been fully clarified. Guidelines [14] recommend that in patients with diabetes associated with hypertension values of 130/ /80 mm Hg or lower should be obtained instead of the regular 140/90 mm Hg; epidemiological data have shown that in PAD the risk is almost as high as in diabetes; therefore, it seems logical to aim at the same target values for blood pressure in patients with hypertension and PAD as for diabetics; however, this issue should be further clarified, as it has not been sufficiently addressed in the literature.

In many PAD patients there are abnormalities in other vessels, such as the arm arteries, causing difficulties in blood pressure measurement. Therefore careful repeated measurement of blood pressure on both arms is essential. The estimation of a long-term prognosis can be improved upon in such high-risk patients by 24-hour ambulatory recordings [15].

Control of cardiovascular risk

Besides blood pressure control, all efforts should be directed toward decreasing total cardiovascular risk. Antiplatelet drugs such as aspirin or clopidogrel should be administered in all PAD patients [6, 9]; as mentioned above, ACE inhibitors have, in a number of studies, been shown to improve claudication distance as well as favourably con-

trolling blood pressure. However, information emerging from the HOPE study has shown that the ACE inhibitor ramipril could also significantly decrease cardiovascular morbidity and mortality in high risk patients [16]. Moreover, the Heart Protection Study (HPS) has convincingly shown that statins are capable of significantly decreasing such risk in this type of patient [17]. This total approach (antiplatelet drugs, statins, ACE inhibitors) obviously requires the use of several drugs besides those necessary for controlling elevated blood pressure; all efforts should therefore be made to improve the compliance of patients to such a treatment regime. Furthermore, cost calculations should be made to see whether the costs of such an approach would outweigh the benefits of controlling the greatly increased risk in these patients.

Conclusion (Table 1)

In PAD patients with hypertension the total CV risk is substantially increased. All efforts should be made to control blood pressure to at least 140/90 mm Hg or even lower, as in diabetic patients. This can be achieved by all antihypertensive drugs; only ACE inhibitors seem to have, besides their blood pressure lowering properties, a slightly more favourable effect on claudication distance than the other antihypertensives. However, the most important measures will aim at decreasing total CV risk; this can be achieved by adding to the antihypertensive treatment antiplatelet drugs, ACE inhibitors and statins.

Table 1. Summary box: Treatment of hypertension in PAD patients

PAD carries an elevated risk of CV morbidity and mortality
Hypertension further increases the risk in PAD patients
Effective control of BP is more important than the choice of specific antihypertensive drug
The management of total CV risk by antiplatelet drugs, ACE inhibitors and statins is essential

References

1. Clement DL, De Buyzere ML, Duprez DA. Hypertension in peripheral arterial disease. Current Pharmaceutical Design 2004; 10: 3615–3620.
2. Duprez D. Natural history and evolution of peripheral obstructive arterial disease. International Angiology 1992; 11: 165–168.
3. Clement DL, Boccalon H, Dormandy J, et al. A clinical approach to the management of the patient with coronary (Co) and/or carotid (Ca) artery disease who presents with leg ischaemia (Lis). International Angiology 2000; 19: 97–125.
4. Kannel WB, D'Agostino RB, Wilson PW, et al. Diabetes, fibrinogen and risk of cardiovascular disease: the Framingham experience. Am Heart J 1990; 120: 672–676.
5. Fowkes FG, Hously E, Riemersma RA, et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. Am J Epidemiol 1992; 135: 331––340.
6. Duprez D, Clement DL. Medical treatment of peripheral vascular disease: good or bad? Eur Heart J 1992; 13: 149–151.
7. Boccalon H, Lehert P, Mosnier M. Effect of naftidrofuryl on physiological walking distance in patients with intermittent claudication. Ann Cardiol Angéiol 2001: 50: 175–182.
8. Spengel F, Clement D, Boccalon H, Liard F, Brown T, Lehert P. Findings of the Naftidrofuryl in Quality of Life (NIQUOL) European Study program. International Angiology 2002; 21: 20–27.
9. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med 2001; 344: 1608–1621.
10. Novo S, Abrignani MG, Pavone G, et al. Effects of captopril and ticlopidine, alone or in combination in hypertensive patients with intermittent claudication. Int Angiol 1996; 15: 169–174.
11. Bogaert M, Clement DL. Lack of influence of propranolol and metoprolol on walking distance in patients with chronic intermittent claudication. Eur Heart J 1983; 4: 203–204.
12. Radack K, Deck C. Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease: a meta-analysis of randomized controlled trials. Arch Intern Med 1991; 151: 1769–1776.
13. Haenni A, Lithell H. Moxonidine improves insulin sensitivity in insulin-resistant hypertensives. J Hypertens 1999; 17: S29–S35.
14. 2003 European Society of Hypertension — European Society of Cardiology. Guidelines for the management of arterial hypertension. J Hypertens 2003; 21: 1011–1053.
15. Clement DL, De Buyzere ML, De Bacquer DA, et al. for the office versus ambulatory pressure study investigators. Prognostic value of ambulatory blood pressure recordings in patients with treated hypertension. N Engl J Med 2003; 348 (24): 2407–2415.
16. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; 342: 145–153.
17. Heart Protection Study Collaborative Group (HPSCG), MRC/BHF Heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7–22.