European Heart Journal Supplements (2002) **4** *(Supplement B),* B58–B62

Coronary artery disease and intermittent claudication: how to manage the patient

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Coexistence of peripheral arterial disease (PAD) and coronary artery disease (CAD) is common. PAD worsens the prognosis of patients with and without CAD. Thus, patients with PAD should be treated for secondary prevention, regardless of the diagnosis of CAD. PAD should be sought in smokers or diabetics aged between 59 and 69 years, in those older than 70 years, in those with known atherosclerotic disease, and in those with suspicion of PAD. As a screening tool, Doppler measurement of the ratio between ankle and arm pressures offers the best approach. Conversely, pharmacological stress imaging should be employed to rule out CAD in PAD patients. Treatment of PAD implies risk factor modification, especially smoking cessation and lipid profile. Pharmacological treatments include preventive drugs and drugs that affect claudication. Unfortunately, few drugs have been proven effective for the latter. These include cilostazol and propionyl-L-carnitine, which ameliorates symptoms and quality of life. It remains unresolved whether different treatment strategies for coexistent CAD impact favourably on prognosis in these problematic patients.

(Eur Heart J Supplements 2002; 4 (Suppl B): B58–B62)

Key Words: Cardiovascular risk, coronary artery disease, peripheral artery disease.

Interaction between peripheral and coronary artery disease

The presence of peripheral arterial disease (PAD) has been long recognized to be associated with an adverse prognosis in patients with and without overt coronary artery disease (CAD)[1,2]. In fact, several studies have reported excess mortality in patients with PAD, almost exclusively due to an excess of vascular and, particularly, cardiovascular deaths. This increase in mortality is most evident in patients with severely symptomatic PAD, but it also occurs in asymptomatic patients[1]. Long-term follow-up studies have shown that only 25% of severely symptomatic PAD patients are alive at 10 years from diagnosis, independently of the concomitant presence of CAD[1]. In patients with known CAD, such as the population evaluated in the Coronary Artery Surgery Study (CASS)[2], the presence of PAD increased cardiovascular mortality by approximately 25% during a 10-year follow-up. Such prognostic data clearly underscore the need to diagnose PAD, especially in patients with CAD.

Classic major risk factors for CAD (smoking, hypertension, diabetes mellitus and hypercholesterolaemia) are associated with the presence of PAD, and the prevalence of cerebrovascular disease and PAD in patients with CAD is particularly enhanced by the concomitant occurrence of two or more of these risk factors[3]. However, among the major cardiovascular risk factors smoking plays by far the predominant role, as indicated by the substantial increase in the prevalence of cerebrovascular disease and PAD in smokers as compared with non-smokers who have another major risk factor[3]. This strong, but not completely explained association between smoking and PAD needs to be emphasized among cardiologists as an additional element of suspicion, and investigation for PAD should be conducted in all smokers with CAD.

The recognition of PAD as a major risk factor for cardiovascular death is still unsatisfactory; this leads to underestimation and under-treatment of many patients with PAD. From a recent retrospective study[4], it emerged that antiplatelet therapy is prescribed to only 50% of claudicant patients. Therefore, an important consequent practical

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1520-765X/02/0B0058 + 05 $35.00/0

implication for the management of these patients should be the implementation of secondary prevention strategies to modify the cardiovascular risk profile, even in those PAD patients without a diagnosis of CAD.

From a pathophysiological standpoint, the reason(s) for excess cardiovascular mortality in PAD patients are not fully understood. Obviously, at least part of the increased risk may be attributable to a more severe extension of the atherosclerotic disease in PAD patients. However, additional mechanisms that are not necessarily correlated to more extensive atherosclerotic disease may also be active. It can be hypothesized that PAD patients have a more severe impairment of endothelial function that leads to a more frequent occurrence of acute coronary syndromes. In addition, abnormal vascular reactivity may contribute to prognosis. Indeed, in our haemodynamic laboratory provocation of limb ischaemia in patients with PAD and concomitant CAD revealed a significant reduction in the diameter of epicardial coronary arteries, as assessed by quantitative coronary angiography, and intra-coronary Doppler-derived blood velocity (unpublished data). This observation is pathophysiologically intriguing because it may indicate an important link between peripheral ischaemia, coronary ischaemia and acute coronary complications.

The prevalence of CAD among PAD patients varies according to the clinical characteristics of the population studied. In our institution, more than 45% of PAD patients had evidence of CAD[4]. However, this figure may increase up to 66% in patients at particularly high cardiovascular risk such as those developing PAD before the age of 40 years[5]. It has also been observed among our patients that the presence of PAD is associated with more extensive CAD, as reflected by the higher percentage of PAD patients with two-vessel or three-vessel CAD as compared with CAD patients without PAD. Consistent with this is that the likelihood of concomitant PAD linearly increases with the severity of CAD, such that PAD is present in more than one-third of patients with severe CAD[5]. Again, this figure is influenced by the population considered. For example, in the Program of Surgical Control of Hyperlipidemia (POSCH) study[6], which included patients with hypercholesterolaemia and previous myocardial infarction, the prevalence of PAD reached 66%. However, the significant prevalence of CAD, even in patients with mild-to-moderately severe CAD, renders it advisable to investigate all CAD patients in order to exclude concomitant PAD.

Diagnostic management

The presence of PAD should be investigated not only in patients with symptoms suggestive of PAD but also in those with other (carotid, renal or coronary) vascular atherosclerotic diseases, and in persons with diabetes and long-term smokers. This is because asymptomatic PAD is even more common than intermittent claudication[7,8] and is often unrecognized, although it is a condition that places the patient at elevated cardiovascular risk[1].

Independently of the presence risk factors, PAD should be excluded in all persons over 70 years old[9]. The most accurate and cost-effective diagnostic screening tool is Doppler measurement of the ratio between systolic blood pressure in the ankle and systolic pressure in the arm (ankle–brachial index [ABI] index). Normal values for ABI lie between 0·91 and 1·30. However, if clinical suspicion remains despite normal ABI under resting conditions, then post-exercise ABI should be measured. ABI values of 0·90 or less are diagnostic for PAD; when ABI is 0·40 or less PAD can be defined as severe, and is potentially a cause of trophic lesions. Further exploration is required in diabetic patients because their arteries are not compressible (and therefore measured pressure is inaccurate). In such patients, big toe pressure and/or colour-Doppler imaging of the peripheral vascular tree is warranted.

Similarly, all PAD patients should be examined for the presence of subclinical CAD. Claudication may often prevent the use of the exercise stress test to rule out CAD. Thus, in all symptomatic PAD patients a pharmacological (dipyridamole, adenosine or dobutamine) stressor in conjunction with imaging (echo or nuclear perfusion) modalities should be employed. Patients with inducible ischaemia should proceed to coronary angiography in the light of the excess cardiovascular risk, and should possibly undergo revascularization. However, it must be recognized that there are no randomized studies that demonstrate that PAD patients benefit more from myocardial revascularization than do similar non-PAD patients.

Treatment of patients with coronary and peripheral arterial disease

Treatment of CAD patients affected by PAD consists of a non-pharmacological and pharmacological approach (Table 1). Of course, modification of risk factors is the first measure to implement, like in all coronary patients. However, it must be emphasized that the impact of risk factor treatment on PAD is different from that on CAD. As noted above, among the conventional risk factors smoking has the most critical impact on PAD severity. In fact, smoking cessation is associated with blunted progression to critical limb ischaemia[10], or even regression of PAD atherosclerotic lesions, and should therefore be strongly pursued. However, it has only minimal or no effect on PAD symptoms[11].

Pharmacological treatment of hypercholesterolaemia is mandatory in patients with low-density lipoprotein cholesterol values in excess of 100 mg . dl^{-1}. It has been reported that treatment of hypercholesterolaemia reduces the progression of atherosclerotic lesions[12]. In addition, treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) also improves symptoms. In fact, the Scandinavian Simvastatin Survival Study (4S) trial[13] showed that, in coronary patients treated with simvastatin, there was a 38% reduction in new or worsening claudication as compared with placebo. This finding is not surprising, considering the role of endothelial dysfunction

Table 1. Management of peripheral arterial disease in patients with coronary artery disease

Treatment type	Treatment
Non-pharmacological	Regular exercise Smoking cessation Overweight correction
Pharmacological treatment	Preventive drugs Antiplatelet (clopidogrel, aspirin, ticlopidine) Ramipril Statins in hypercholesterolaemic patients Drugs for claudication Propionyl-L-carnitine Cilostazol Pentoxifylline (unproven efficacy) Oral prostaglandins (uncertain efficacy)

in the pathogenesis of claudication and the beneficial effects of simvastatin on endothelial dysfunction[14]. Patients with PAD exhibit impaired synthesis of nitric oxide[15], and it has recently been reported that periodic intravenous infusion of L-arginine (which restores nitric oxide concentrations) significantly improved haemodynamic and clinical parameters in PAD patients[16]. In contrast, tight control of blood glucose level in diabetic patients does not impact on the progression or clinical manifestations of PAD[17]. Similarly, there is no convincing evidence that treatment of hypertension favourably influences PAD[9].

It has been reported that in patients at risk for cardiovascular events, including those with PAD and an additional major risk factor, treatment with ramipril dramatically reduces cardiovascular mortality and morbidity over a 5-year follow-up. Subgroup analysis of the Heart Outcomes Prevention Evaluation (HOPE)[18] trial showed that patients with PAD were at increased cardiovascular risk (22% of events in PAD patients versus 14% in non-PAD patients). In those patients with PAD (representing more than 42% of the entire study population), treatment with ramipril was associated with an even greater substantial reduction in cardiovascular mortality and morbidity as compared with that in non-PAD patients. Thus, the results of that trial suggest that patients with PAD may benefit from administration of ramipril 10 mg . day^{-1}.

Antiplatelet drugs (aspirin, ticlopidine, or clopidogrel) are mandatory in CAD patients with and without concomitant PAD. Recently, in a study that compared aspirin with placebo in patients with PAD or previous myocardial infarction or stroke[19], clopidogrel at a dose of 75 mg . day^{-1} was significantly more effective than aspirin in reducing the incidence of myocardial infarction, stroke or cardiovascular death. In fact, the advantage of clopidogrel over aspirin reported in that trial was entirely due to the benefit observed in patients with PAD. Although the reasons for this observation are unclear, these data clearly indicate that clopidogrel should be the preferred antiplatelet drug in patients with PAD.

With respect to the drugs commonly used for symptomatic angina in CAD patients, those agents are ineffective for treatment of claudication. A randomized, double-blind, placebo-controlled, crossover study[20] showed that acute administration of glyceryl-trinitrate improved maximal walking distance only by 1%. Similarly, no effect on walking capacity was achieved in claudicant patients receiving nifedipine[21]. However, the use of this calcium channel blocker combined with atenolol produced a modest but significant decrease in maximal walking capacity. In effect, it has long been claimed that beta-blockers should not be used in PAD patients because of their potential vasoconstrictive action, which could lead to worsening of symptoms. However, there are no controlled studies that document a significant negative effect of these drugs on claudication, and a meta-analysis of the most relevant studies conducted in PAD patients[22] revealed no detrimental effects. Therefore, beta-blockers can safely be used in the vast majority of PAD patients without trophic lesions. Caution should be used only in the most advanced forms of the disease.

Effective treatment of claudication can be achieved by regular exercise. A meta-analysis of 21 controlled studies that compared a programme of regular moderate exercise with placebo[23] clearly indicated that exercise improves both the time to initial claudication and the maximal walking distance in PAD patients. Supervised exercise training should be strongly encouraged in patients with CAD and PAD. In fact, it has been demonstrated that regular exercise is important for secondary prevention in CAD patients, because it reduces total and cardiovascular mortality, and the number of non-fatal coronary events, and slows the progression of coronary atherosclerosis[24].

The use of specific drugs for treatment of claudication can be very disappointing. Pentoxyfilline, a drug that has been widely used, has never been shown to provide effective benefit in controlled studies and may have only a minimal clinical effect in selected patients[25]. Oral prostaglandins have been reported to be effective in recent studies, but their role in the long-term treatment of claudication remains undetermined[9]. The only drugs with proven beneficial effects are cilostazol and propionyl-L-carnitine.

Cilostazol is a 3-phophodiesterase inhibitor that acts by raising intracellular cyclic adenosine monophosphate levels. A review of the most relevant trials[9] clearly indicated that this drug is effective as compared with placebo or pentoxifylline. However, side effects (headache, diarrhoea, dizziness and palpitations) are very common. Furthermore, cilostazol should not be given to claudicant patients with heart failure, given the negative experience with milrinone, another phosphodiesterase inhibitor.

Introduction of propionyl-L-carnitine marked an innovative approach to treatment of PAD. In fact, this drug has no haemodynamic effects and its beneficial action is due to its metabolic effects, mainly represented by enhanced intracellular energy production because of increased availability of both intracellular carnitine and substrates for energy production. As shown in Table 2, three large multicentre

Table 2 Propionyl-L-carnitine in intermittent claudication

Study	Number of subjects	Baseline walking capacity (m)	Improvement over placebo		Quality of life
			ICD	MWD	
Brevetti *et al.*[26]	214	30–400	+57% (ns)	+59% ($P < 0.05$)	Improved
Brevetti *et al.*[27]	173	≤250	+94% ($P < 0.05$)	+81% ($P < 0.01$)	Improved
	155	>250	–12% (ns)	–18% (ns)	Not Improved
Hiatt *et al.*[28]	155	50–250	+95% ($P < 0.01$)	+100% ($P < 0.001$)	Improved

ICD=time to initial claudication; MWD=maximal walking distance; ns=not significant.

randomized, placebo-controlled studies[26–28] have reported that propionyl-L-carnitine significantly increases the time to initial claudication and the mean distance walked as compared with placebo. These effects were sustained over a 1-year follow-up[27] and were associated with a significant improvement in quality of life[29]. Interestingly, the effects of the drug were evident only in patients with more severe symptoms (i.e. those unable to walk more than 250 m)[27].

For patients with trophic lesions (Fontaine stage IV) or with disabling symptoms despite optimal medical therapy and smoking cessation, percutaneous or surgical revascularization remains the only alternative when appropriate.

Conclusion

The presence of PAD confers an ominous prognosis on patients with CAD, and therefore such patients need to be identified and treated even more aggressively than patients with CAD only. However, many unanswered issues remain for CAD patients with concomitant PAD. Pharmacological treatment of CAD is well established, and in recent years medical therapy of claudication has improved with the introduction of new drugs that are effective in reducing disability. The drugs used for treating one condition are safe, but inefficacious for the other. This often leads patients and doctors to neglect therapy for claudication. Furthermore, medical treatment of claudication has improved in recent years, but many unanswered issues remain for PAD patients with concomitant CAD. Furthermore, given the impressive association with increased cardiovascular mortality and morbility, it is not entirely clear how and whether this adverse prognosis can be influenced by different treatment strategies. This uncertainty is due to the lack of randomized trials focused on the management of CAD patients with concomitant PAD, which will be more than welcome in the future.

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