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Peripheral Arterial Occlusive Disease – an Interdisciplinary Approach

E. Groechenig

Abstract: Vascular diseases are the most common diseases and the most common causes of death in developed countries. Many medical disciplines deal with vascular diseases and there is no strict and clear concept in education and training of these physicians. In German-speaking countries "angiology" was established several years ago. The angiologist is a highly qualified physician, who, in most cases, comes from internal medicine (a minority from dermatology). Although peripheral arterial disease (PAD) is the most frequent disease angiology deals with, the angiologist has to have a broad knowledge of general vascular medicine and has to be qualified in all diagnostic and therapeutic procedures. PAD is just like the tip of an iceberg and has to be mentioned as a severe disease with a bad overall prognosis similar to that of Duke-B colon carcinoma. So, global access with staging and grading of atherosclerosis, evaluation of concomitant diseases, control of risk factors and adequate treatment of PAD is the gold standard. Therefore, several medical

specialities are involved with the angiologist functioning as the integrative "general manager" between the disciplines for the welfare of the patient.

Kurzfassung: Periphere arterielle Verschlusskrankheit – ein interdisziplinärer Ansatz. Gefäßkrankheiten sind die häufigsten Erkrankungs- und Todesursachen in den industrialisierten Ländern. Gefäßkrankungen können sich an verschiedensten Organen manifestieren und dazu führen, daß unterschiedliche medizinische Disziplinen damit beschäftigt werden, ohne daß häufig eine gefäßspezifische Ausbildung vorhanden ist. Um diesem Umstand Rechnung zu tragen, wurde in den deutschsprachigen Ländern vor einigen Jahren der Additivfacharzt für Angiologie eingeführt. Der Angiologe ist ein hochqualifizierter Spezialist mit einer internistischen (seltener dermatologischen) Basisausbildung. Der Angiologe hat einerseits ein breites Wissen über die allgemeine Gefäßpathologie und -physio-

logie, kennt die verschiedensten diagnostischen und therapeutischen Verfahren und hat andererseits Kenntnis von der entsprechenden Organpathologie.

Die periphere arterielle Verschlusskrankheit (PAVK) ist zwar das häufigste Krankheitsbild, mit dem der Angiologe konfrontiert wird, sie stellt jedoch sozusagen nur die „Spitze des Eisberges“ dar. Die PAVK mag zwar klinisch gutartig und mild verlaufen, ist aber im Grunde wegen der häufig generalisierten Atherosklerose eine Erkrankung mit schlechter, dem Duke-B-Kolonkarzinom vergleichbarer Prognose. Diese Patienten brauchen eine umfassende Betreuung mit Staging und Grading der Atherosklerose, Erfassen von Begleiterkrankungen und Risikofaktoren sowie adäquater Behandlung der PAVK. Die Betreuung eines gefäßkranken Patienten erfordert häufig die Zusammenarbeit mit verschiedenen Disziplinen, wobei dem Angiologen die Rolle des Koordinators und Generalmanagers zukommt. **J Kardiol 2003; 10: 139–41.**

Introduction

Life starts with a vessel, and in most cases, life ends with a vessel. The most important thing for vascular homeostasis is the integrity of the endothelium. Any vascular disease shows destruction of endothelium with decreased or destroyed function as the beginning of a vicious circle. The pathophysiology of any vessel disease is uniform (Fig. 1).

Structural changes in vessels always go along with defective endothelial function. The impaired formation of vasodilatory substances (NO, endothelium derived hyperpolarizing factor, prostacyclin) or other substances which inhibit platelet activation and adhesion, lead to further disorders of the circulation and eventually promote the development of vascular disease.

The dysfunction of the endothelium leads to the release of substances which promote the immigration and replication of smooth muscle cells in the vessel wall. This in turn produces substances which autonomously regulate the tone of the smooth muscle cells and other substances and these promote the replication and formation of local thrombi. The different factors, such as increase in pressure, shear stresses, hypoxia, acidosis and an increased concentration of free radicals, lead to structural changes in the vessel wall. The impaired function is expressed by a decreased production of prostacyclin, denoting endothelial damage and an increased concentration of thromboxane A₂, indicating an augmented activation of platelets.

The formation of atherosclerosis is promoted by endothelial injury and activation of different cell types. Blood platelets adhere to the damaged endothelium. Monocytes, which infiltrate the endothelium, accumulate lipids and change into foam cells. These different cell types release growth factors, which are probably identical to those which act on the smooth muscle below the endothelium and cause it to proliferate. Lipid per-

oxides are very potent and selective inhibitors of prostacyclin formation. Very high concentrations of lipid peroxides (eg, 15-hydroxyperoxy-arachidonic acid) occur in sclerotic vessel lesions. Lipid peroxidation caused by formation of free radicals occurs with vitamin E deficiency, ageing and in the presence of hyperlipidaemia. The accumulation of lipid peroxide in atheromatous plaques promotes thrombus formation by inhibition of prostacyclin formation in the endothelium without influencing thromboxane A₂ formation in thrombocytes. In addition, thrombocyte aggregation is induced by lipid peroxides such as 15-hydroperoxy-arachidonic acid. Prostacyclin is not produced in human atheromatous plaques. It has been shown in animal experiments that prostacyclin synthesis increases with denudation of the endothelium of the aorta and during re-endothelialization. This recovery of the endothelium was not observed in animals with mild hypercholesterolaemia.

Independently of the organic manifestation we call this disease "arterial occlusive disease" and suggest distinguishing between:

- peripheral arterial (occlusive) disease (PAD)
- coronary arterial (occlusive) disease (CAD)
- cerebrovascular arterial (occlusive) disease (CVAD)
- visceral arterial occlusive disease (VAD)

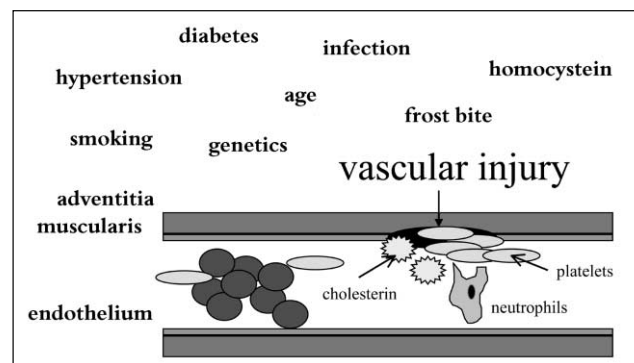


Figure 1: Pathophysiology of vascular diseases

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Incidence of Peripheral Arterial Disease

Estimates of the incidence of PAD in a population are subject to a number of errors, because only a minority of patients with demonstrable PAD complain of symptoms. Many patients with symptoms of PAD are elderly considering their symptoms as parts of growing old and therefore they do not speak to their doctor. Another fact is, that in rural communities 50 % consult their general practitioner, whereas in cities only 10 % do [1], but most patients with PAD are not referred to a specialist, and therefore incidences based on hospital referrals are grossly underestimated [2] (Fig. 2).

Prevalence of PAD

Prevalence rates also differ depending on the study population and the diagnostic methods used. So the prevalence for symptomatic PAD varies from 0.4–14.4 % [2], whereas the prevalence for asymptomatic PAD ranges in several studies from 0.9 % to 22 % [3–8].

Risk Factors for Developing PAD

The development of PAD is caused by similar risk factors as with other atherosclerotic diseases (Fig. 3).

Diabetes

Diabetes is an important risk factor for the development of atherosclerosis, which becomes clinically manifest 5–10 times more often in diabetic patients than in non-diabetics [9]. Diabetic atherosclerosis is more diffuse, more severe and manifests itself at an earlier age [10, 11].

Diabetic patients show signs of PAD twice as often as non-diabetic patients [12]. PAD in patients with diabetes is more aggressive and shows large vessel involvement early coupled with microangiopathy. Patients with PAD and diabetes show a 35 % risk of sudden ischaemia (in non-diabetics = 19 %) and a 21 % risk of major amputation (non-diabetics = 3 %) [13].

The UKPDS has shown that intensive glycaemic control provided a significant reduction in any diabetes endpoint (largely microvascular) and myocardial infarction. Use of metformin was also associated with a reduction in diabetes end-points, all-cause mortality and myocardial infarction. But the risk of PAD could not be influenced by intensive treatment and so intensive glycaemic control alone is insufficient to prevent PAD which

underlines the importance of aggressive control of the other risk factors. Nevertheless, patients with diabetes and peripheral arterial disease should have aggressive control and normalization of blood sugar. Fasting blood sugars should range from 80–120 mg/dl, and postprandial sugars should be < 180 mg/dl, HBA_{1c} should be < 7.0 % [14, 15].

Smoking

A diagnosis of PAD is made up to a decade earlier in smokers than in non-smokers, and smokers show more proximal atherosclerotic lesions than non-smokers [11].

In the Framingham Study the risk at all ages was almost double for PAD compared with coronary involvement. Cigarette smoking increases the risk of PAD in both sexes and heavy smokers show a fourfold risk of developing PAD [16].

Smoking cessation is associated with a rapid decline in the incidence of PAD. The risk for ex-smokers 1 year after quitting is approximately the same as that for non-smokers [17, 18].

Hypertension

Hypertension carries a 2.5-fold age-adjusted risk in men and a 3.9-fold age-adjusted risk in women [16]. The effects of the treatment of hypertension on the natural history of PAD have not been evaluated. Nevertheless, patients with PAD should have a treatment for hypertension according to the Joint National Committee guidelines [19], because hypertension is a more important life-threatening risk factor than PAD.

Dyslipidaemia

Treatment of dyslipidaemia reduces the progression and the incidence of PAD [20, 21].

Coexisting Vascular Disease

Because PAD, coronary artery disease and cerebrovascular disease are all manifestations of atherosclerosis, it is not surprising that these three conditions commonly occur together.

The frequency of these diseases depends on the sensitivity of these diagnostic procedures used. If coronary angiography is used for diagnostics, the prevalence of coronary artery disease is as high as 90 % [22].

Duplexsonography has found carotid disease in 26–50 % of PAD-patients [23, 24].

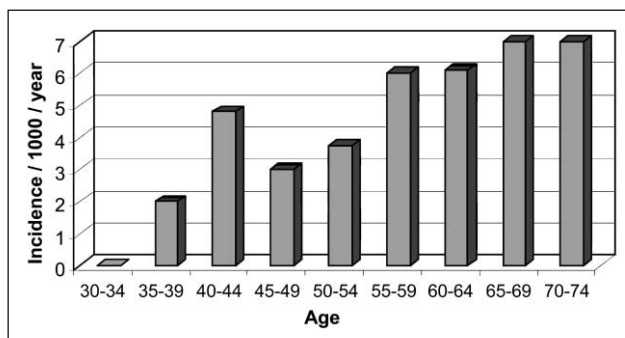


Figure 2: Incidence of peripheral arterial disease

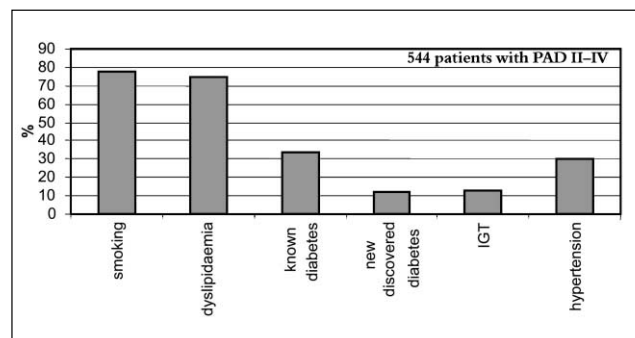


Figure 3: Risk factors for PAD development

■ Natural Progression of PAD

PAD is a progressive disease, despite its benign clinical course in most cases. Angiographic progression of the disease can be documented in 63 % of patients five years after the initial diagnosis. Of those, who had survived for 5 years after the diagnosis, 66 % still had no limiting symptoms of PAD [25]. The stabilization may be due to the development of collaterals, metabolic adaptation of ischaemic muscle by an increase in aerobic enzyme content and capillary density or the patient altering the gait to favour non-ischaemic muscle groups.

25 % of patients with PAD will deteriorate, 7–9 % during the first year after diagnosis and 2–3 % per year thereafter [26]. 7 % of patients with PAD will have a major amputation after 5 years and 12 % after 10 years [27].

The risk of progression to severe ischaemia or limb loss is higher, the lower the ankle-brachial-pressure-index (ABPI) is. In the group of ABPI from 40–60 mmHg for example it is 8.5 % [28].

Patients with asymptomatic or symptomatic PAD have widespread arterial disease and carry an increased risk of stroke, myocardial infarction and cardiovascular death. The annual incidence of non-fatal myocardial infarction is estimated to be 8.2 % and of cerebrovascular disease 6.8 % [29]. 2–4 % of PAD-patients have a non-fatal cardiovascular event within the first year, but the information hereof is very limited.

The 5-years mortality rate is 30 %, the 10-years mortality rate 50 % and the 15-years mortality rate is as high as 75 %, so that the prognosis of PAD is comparable to that of Duke-B colon carcinoma. Coronary artery disease is with 40–60 % by far the most common cause of death. Other causes are cerebrovascular disease with 10–20 % and other vascular events, mostly ruptured aortic aneurysm in 10–20 %. 20–30 % of patients with PAD die of non-cardiovascular causes.

■ Therapeutic Options

The most important fact in the management of the PAD-patient is to consider that these patients are at significant risk for developing severe and often fatal cardiovascular complications. Thus, their most serious problem is not the limitation of walking, but the 2–4 times higher risk of dying from the complications of generalized atherosclerosis.

So, similar to oncology, treatment decisions have to be based on the complete staging and grading of the atherosclerotic disease. Risk factor modification, antiplatelet therapy and regular exercise training should be offered as basic management in all patients with PAD.

The decision to consider a patient for interventional therapy depends on the patient's existing disability compared to the

procedural risk and likelihood of long-term success of the procedure. Before offering the option of any invasive therapy the following considerations must be taken into account:

- no response to exercise therapy and risk factor modifications
- severe disability, which is characterized by the inability to perform normal work or having serious impairment of other activities important to the patient
- absence of concomitant diseases, which would limit exercise even if claudication was improved
- low risk, initial and long term success should be predictable
- the patients anticipated natural history and prognosis.

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