Part X

Factors influencing results

Cardiovascular Risk Factors in Patients With Critical Leg Ischemia

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Chronic critical leg ischemia (CLI) is an extremely severe clinical condition which poses the patient at high risk for limb loss. However, because of the systemic nature of atherosclerosis and its evident aggressiveness, patients with CLI have been shown to be also at high risk of early and late cardiovascular events and death. It is self-evident that the chronic, progressive nature of atherosclerosis should require continuous care that should start from the preoperative period in order to optimize the immediate and long-term results of lower limb revascularization.

Extensive studies have been carried out to elucidate the risk factors leading to such a condition and whether correction of them could improve immediate and long-term outcome after arterial revascularization. Unfortunately, recent surveys showed that just a minority of these patients are adequately treated according to their cardiovascular risk factors (1-3), and it is also unclear whether patients are adequately evaluated for such risk factors.

The aim of the present chapter is to summarize the current knowledge on cardiovascular risk factors that may mine the success of arterial revascularization for CLI, leading to graft failure, limb loss and/or death, and to provide information on the efficacy of measures to correct these factors.

Coronary artery disease

Atherosclerosis is a generalized disease which is associated with low expectancy of life, especially in patients with extensive occlusive disease of the lower limb arteries, since the worse the lower limb ischemia, the poorer the prospects of survival (4-8).

Biancari et al. (5) showed that, in patients who underwent femorocrural bypass surgery for CLI, the sum of angiographic scores of crural arteries was predictive of long-term survival ($p=0.003$ according to multivariate analysis). Patients who had a completely open outflow artery or with stenoses of < 20% throughout its length had a 5-year survival of about 90%, whereas patients with more severely diseased outflow artery had a survival rate of about 50% ($p=0.008$) (5). Batt et al. (4) reported a significant correlation between the angiographic findings of infrapopliteal atherosclerotic disease and the survival outcome as well.

Dawson et al. (6) reported a 5-year cardiac survival rate after infrainguinal bypass surgery for CLI of 73%, whereas it was 91% among claudicants ($p<0.001$). Taylor and Porter (9) observed an even larger difference in the 5-year survival outcome, being 30% in patients with CLI and 67% in claudicants ($p<0.005$).

Coronary artery disease is recognized as the main source of perioperative and late cardiac morbidity and mortality in patients undergoing lower limb revascularization. L'Italien et al. (10) observed that patients who underwent infrainguinal revascularization had a more than 2-fold increased risk to experience a perioperative fatal or non fatal cardiac event (13% vs. 6%) and a 3-fold increased risk of late cardiac events (at 4 years, 74% vs. 90%) and long-term mortality (at 3 years, 91% vs. 81%) when compared with patients who underwent aortic surgery, which is commonly considered as a major surgical procedure. Krupski et al. (11) did not observe such an increased risk of immediate postoperative cardiac complications, but cardiovascular events were significantly more frequent during long-term follow-up in patients who underwent infrainguinal revascularization than in those who underwent aortic surgery (25% vs. 8%, $p=0.04$). These studies showed that such an increased risk in patients undergoing lower limb ischemia is due to the coexistence of other severe comorbid diseases, especially coronary artery disease and diabetes, which, therefore, makes infrainguinal revascularization as risky as (or even riskier than) a major surgical procedure such as open abdominal aortic aneurysm repair (10,11).

Attempts to improve the outcome of patients with lower limb ischemia have been directed toward preoperative detection and treatment of coronary artery disease. Several studies (12-19) demonstrated the benefits of endovascular and surgical revascularization of the myocardium before peripheral vascular surgery which resulted in excellent postoperative cardiac morbidity and mortality rates. Some authors proposed an aggressive screening for coronary artery disease and myocardial revascularization also in asymptomatic patients undergoing vascular surgery (15,17).

Hertzer et al. (15) reported the largest series of patients undergoing peripheral vascular surgery who were screened for coronary artery disease and even-

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tually underwent coronary artery bypass surgery before vascular procedure. In their study, patients who did not undergo coronary revascularization before infrainguinal revascularization had an operative mortality rate of 4.5%, whereas it was nil in those who first underwent coronary bypass surgery (15). However, the authors did not report any information about the indication for infrainguinal revascularization and how many patients underwent prophylactic coronary revascularization.

Although it has been shown that prophylactic CABG confers protection against cardiac events following peripheral vascular surgery and prolongs life-expectancy (20), the benefits can be achieved only by those who survive coronary bypass surgery without postoperative morbidity, since the latter may preclude a vascular procedure (21-23). Furthermore, lower limb arterial disease is a major preoperative risk factor for poor postoperative outcome after coronary artery bypass grafting (24,26-28), especially because patients with CLI have a high incidence of severe comorbid conditions such as diabetes and chronic renal failure, which further increase the risk of cardiac surgery (21,24).

The operative mortality after prophylactic myocardial revascularization before peripheral vascular surgery may approach 7% (15,17), but in some clinical series it may be over 10% (27,29). This observations masks the potential benefits of prophylactic surgical revascularization of the myocardium, since the mortality rate after infrainguinal bypass surgery for CLI is generally below 5%. Percutaneous transluminal coronary angioplasty, when feasible, probably represents a valid alternative since may be associated with lower morbidity rate (14).

Krupski et al. (22) reported the results of 42 patients scheduled to undergo peripheral vascular surgery who underwent preoperative cardiac evaluation. Thirty-eight percent of them had adverse events related with cardiac evaluation, percutaneous transluminal angioplasty and coronary artery bypass grafting. Eight patients (19%) refused to undergo vascular procedure after cardiac work-up (discomfort being the main reason), two patients with CLI had limb loss because of delay due to cardiac evaluations (5%), two had pseudoaneurysm (5%), one had prosthetic infection (2%), one had sternal infection (1%), one had renal failure (1%) and another experienced anoxic brain injury (2%). Two patients (5%) died postoperatively. On the contrary, the postoperative mortality rate in patients who did not undergo such an extensive preoperative cardiac evaluation was 2.3%.

These considerations have led some authors (22,30,31) to restrict extensive preoperative evaluation only to claudicants since in these patients lower limb revascularization is not urgent and is an option.

von Knorring (32) observed that hypotensive episodes during anesthesia were associated with postoperative myocardial infarction occurring during the day of surgery or on the first postoperative day in 33% of patients at highest risk for transmural infarction. This observation and further studies on this topic showed that the choice of anesthesia technique, surgical stimuli, hypovolemia, reversal of neuromuscular blockade, postoperative hypothermia, pain, hypoxia, anemia and disturbances of electrolytes may significantly contribute to perioperative cardiovascular events after peripheral vascular surgery (33-35). From and anesthesiologic point of view, these factors can be favorably modified as it has been clearly demonstrated that optimization of cardiac function and oxygen delivery can significantly reduce postoperative morbidity and mortality rates in high risk surgical patients (35,36).

Berlauk et al. (36), in a prospective, randomized study on preoperative cardiovascular hemodynamics optimization using pulmonary artery catheterization, showed that this method significantly decreased postoperative morbidity and mortality in 89 patients undergoing *in situ* vein bypass grafting for CLI. Interestingly, the use of preoperative pulmonary catheterization was associated also with better early bypass graft patency. Therefore, there is evidence that optimizing cardiovascular hemodynamics preoperatively, and adequate anesthesia and intensive care management could significantly decrease the postoperative mortality and morbidity rates, at least during the immediate postoperative period, probably even more effectively than prophylactic myocardial revascularization.

Cerebrovascular disease

Little information is available on the incidence and the impact of cerebrovascular disease on the outcome of patients with lower limb ischemia. Newman et al. (37) showed that low ankle/brachial blood systolic pressure indexes (ABI) are significantly associated with a carotid stenosis>75%. Gentile et al. (38) reported an incidence of hemodynamically significant asymptomatic carotid artery stenosis of 28.4% in patients undergoing infrainguinal bypass surgery. Zheng et al. (39) observed a statistically significant association between history of stroke/transient ischemic attacks and an ABI<0.90 among men (OR age-adjusted, 4.2 to 4.9 according to race), whereas such an association was weaker among women. Furthermore, also the incidence of preclinical carotid plaque was significantly higher in subjects with ABI<0.90 (OR age-adjusted, up to 2.6 in african-american men) (39).

These observations simply confirm the systemic nature of the atherosclerotic disease, which seems to be fairly advanced in patients with lower extremity ischemia. However, since only a few studies paid enough attention to the prognostic impact of cerebrovascular

disease in patients with lower limb ischemia, it is not clear whether the presence of asymptomatic carotid stenosis or history of transient ischemic attacks and stroke affects the outcome of patients with lower limb ischemia.

In the study by Limburg et al. (40) including patients who underwent several non-cardiovascular surgical procedures, previous cerebrovascular disease was predictive of postoperative ischemic stroke (OR, 12.57), and the risk was particularly high also among patients with peripheral vascular disease (OR, 5.35).

In the study by Biancari et al. (41), history of stroke was predictive of immediate postoperative mortality after infrapopliteal bypass surgery (OR, 3.03). In this series, 7.4% of patients with previous stroke and 1.8% of patients without previous stroke experienced stroke postoperatively (p=0.02). Twelve percent of patients with a history of stroke died postoperatively (p=0.01). When a history of stroke was associated with history of angina pectoris and/or myocardial infarction, the postoperative cardiovascular mortality rate was 22.2%, whereas it was 8.9% among patients with history angina pectoris and/or myocardial infarction alone (p=0.05) (41).

There are a few studies indicating that patients with lower limb ischemia and history of stroke have significantly lower long-term survival rates (42,43). The I.C.A.I. study showed that patients with CLI having a history of stroke had a relative risk of 1.82 for late death. However, in the study by Ogren et al. (44) the presence of carotid stenosis did not add further risk for late cardiovascular events. However, these authors showed that the risk of cerebrovascular events at 10-year follow-up was three times higher in subjects with an ABI<0.9 compared with those having a normal ABI (p<0.001), the former having also a 2.5 times higher risk of cardiovascular death. According to univariate analysis, also subjects with carotid stenosis>30% had a significantly increased rate of cardiovascular mortality as compared with those without carotid stenosis, but its impact on the long-term outcome was not significant at multivariate analysis, leg artery disease being the main predictor of outcome (OR for cardiovascular mortality, 2.0; OR for cerebrovascular event 2.0).

These data suggest that more extensive investigation is required to define the incidence and the impact of asymptomatic and symptomatic cerebrovascular disease in patients with different degrees of lower limb ischemia.

Diabetes

Diabetes is known as a formidable risk factor for the development of accelerated atherosclerosis, and CLI occurs in a large number of diabetic patients because of the frequent and characteristic pattern of this disease which preferentially involves the crural vessels (45). Because of the high incidence of coronary artery disease and cerebrovascular disease, diabetics are at high risk of fatal and non fatal cardiac events, especially after infrainguinal bypass surgery (10,11).

Although in a large series evaluating the immediate postoperative results of infrapopliteal bypass surgery diabetics did not have an increased risk for postoperative cardiovascular mortality (41), Biancari et al. (46,47) observed that diabetics had significantly lower long-term survival rates after femorocrural and popliteal-to-distal bypass surgery for CLI.

Dawson et al. (6) reported a 5-year cardiovascular survival rate of 65% in diabetics and 87% in non-diabetics (p<0.001) after infrainguinal bypass surgery. Hertzer (48) reported an overall 11-year mortality rate after lower limb revascularization of 55% in diabetics and 33% in non diabetics patients (p<0.01), the incidence of fatal myocardial infarction being significantly more frequent among diabetics (37% vs. 15%, p<0.001).

Such a high risk for development of cardiac events is mainly due to coexistent and often unrecognized severe coronary artery disease. In fact, it has been reported that the 7-year rate of cardiac deaths in diabetics without previous myocardial infarction is as high as the rate among non diabetics with a history of myocardial infarction (49), thus suggesting the high incidence of silent, unrecognized severe coronary artery disease among diabetic patients. It seems that in diabetics, the classic manifestation of chest pain associated with myocardial ischemia is absent because of associated cardiac autonomic neuropathy (50,51). Valensi et al. (51), in a 4.5-year follow-up study, reported a statistically significant association between cardiac autonomic neuropathy and the occurrence of late major cardiac events in 120 diabetic patients with no history of myocardial infarction or angina, a normal 12-lead electrocardiogram at rest, and at least two additional cardiovascular risk factors (silent myocardial ischemia-adjusted OR, 4.30).

It is worth of noting that diabetics have also a relative risk of 2.75 to die of non-cardiovascular diseases such as infectious and metabolic complications (52). Eastman and Keen (52) underlined the importance of aggressive correction of dyslipidemia and high arterial pressure combined with intensive glycemic control, protection against non-cardiovascular-disease, smoking cessation, reduction of obesity, restriction of fat and alcohol consumption and increased physical activity to improve the survival outcome of diabetics. In a simulation analysis, these authors calculated that intensive treatment of these factors and elimination of non-cardiovascular causes of death (vaccination reducing the infectious complications and improved glycemic control

reducing non-cardiovascular-disease renal mortality) lead to an increase of life expectancy in 50-year-old diabetic subjects from 18.3 years to 28.1 years, a rate close to the 29.3 years of life expectancy of non-diabetics (52).

Hyperlipidemia

Epidemiological data provided evidence of an association between cholesterol levels and the development of atherosclerosis which led to extensive studies on the role of life-style and dietary modification and the effectiveness of several drugs in reducing the serum levels of total cholesterol and LDL-cholesterol and, thus, the development of atherosclerosis and its complications. Statins have been shown to reduce the risk of cardiovascular events and death and, interestingly, large clinical trials suggested that aggressive lipid-lowering treatment significantly delays atherosclerosis progression and, consequently, the failure of saphenous vein grafts in patients who underwent coronary artery bypass grafting (53,54).

Although it has been shown that hypercholesterolemia is not strongly associated with the development of stroke, results from recent trials on lipid-lowering treatment employing statins have shown that these drugs can also reduce the incidence of non-hemorrhagic stroke (55,56). Interestingly, it seems that statins do not just lower cholesterol. In fact, these drugs may prevent cardiovascular events through a variety of mechanisms including plaque stabilization (57), anti-inflammatory effect (58), endothelial protection (59) and antithrombotic effect (60).

Experimental studies have shown that hypercholesterolemia is associated with the development of intimal hyperplasia of both vein and prosthetic graft (61-63). These observations suggest that dyslipidemia may have a significant impact on the bypass graft patency other than simply causing progression of atherosclerosis in the outflow arteries. However, despite this body of evidence and the fact that hyperlipidemia may occur in more than 40% of patients undergoing infrainguinal revascularization, it has been shown that patients with peripheral vascular disease and hyperlipidemia are significantly less advised and treated with cholesterol-lowering drugs than patients with coronary artery disease (2). Furthermore, this risk factor is not generally taken in consideration in prospective studies evaluating the outcome of patients undergoing infrainguinal bypass surgery.

Prothrombotic states

During the last decade, several studies have shown that hypercoagulable states may have a great impact on the development of coronary and peripheral artery disease leading to severe cardiovascular events (64-72) as well as poor results after revascularization of the lower limb (73-76). These syndromes include disorders of the fibrinolytic system, deficiencies of the natural anticoagulant mechanisms, increased levels of coagulation factors, presence of lupus anticoagulant or anticardiolipin antibodies, and increased platelet reactivity.

Disorders of the fibrinolytic system

It has been shown that patients with lower limb ischemia have abnormal upregulation of both coagulation and fibrinolytic activity as shown by increased levels of D-dimer, fibrinogen, tissue plasminogen activator (t-PA), plasminogen activator inhibitor-1 antigen (PAI-1) and von Willebrand antigen (64-66,68,69, 71,72,77).

Salomaa et al. (77) showed that impaired fibrinolysis may play a role in the early development of atherosclerotic disease probably mediating the effects of other cardiovascular risk factors. Ridker et al. (78) confirmed that such derangements in coagulation are on the long-run associated with development of clinically symptomatic atherosclerotic disease. In their 5-year follow-up study, mean baseline tPA was significantly associated with higher risk of development of late stroke. The age-adjusted relative risk for total stroke and thromboembolic stroke in patients with a mean tPA level in the 95th percentile was 3.51 and 3.89, respectively. A recent study by Johansson et al. (79) confirmed Ridker and colleagues' findings, baseline levels of tPA and tPA/PAI-1 complex being significantly associated with first-ever stroke. In particular, tPA/PAI-1 complex was found to be a strong predictor of all stroke cases and especially of hemorrhagic stroke. Kario et al. (80) have shown that hypercoagulability is a strong risk factor for development of asymptomatic lacunar stroke and the severity of derangement in fibrinolytic activity correlates with the extent of such strokes.

Thompson et al. (72) coupled such observations in patients with coronary artery disease. In their study, fibrinogen and tPA levels correlated with the extent of coronary artery disease and the association between the levels of fibrinogen, tPA and von Willebrand antigen and the risk of subsequent coronary event was strong, the odds ratio being over 2 in the three upper quintiles of fibrinogen and in the upper quintile of tPA. Huber et al. (81) reported significantly higher levels of PAI-1 and tPA in patients with symptomatic coronary disease than in subjects with normal coronary angiograms. Moss et al. (82) reported a 26-month follow-up study analyzing the risk factors associated with recurrent coronary events among 1045 patients enrolled 2 months after myocardial infarction. The Cox model analysis showed that high levels of D-dimer were associated with a hazard ratio of 2.43 for the development of recurrent coronary events.

Lowe et al. (83) showed that blood viscosity and fibrinogen correlated with the degree of ABI, and a positive interaction between levels of fibrinogen and smoking was found, and the Rotterdam Study confirmed that plasma fibrinogen was significantly associated with severe peripheral arterial disease as diagnosed by an ABI<0.70 (OR, age and sex adjusted: 1.63, multivariate, 1.34) (84). Fibrinogen was also found to be higher in patients with critical leg ischemia compared with claudicants, and significantly associated with restenosis after primarily successful percutaneous transluminal angioplasty for lower limb ischemia (85). Pedrinelli et al. (86) reported the important finding of increased risk of cardiovascular death in patients with CLI and high plasma fibrinogen levels, thus suggesting that a prothrombotic state is a major determinant of survival outcome in patient with such a severe ischemic condition.

Levy et al. (87), in a prospective study evaluating risk factors in young adults with premature lower extremity atherosclerosis, observed that defective fibrinolytic activity was the most common hypercoagulability condition, being found in 59% of cases. Fibrinolytic abnormalities were significantly associated with prior vascular surgical procedures and history of coronary artery disease.

Recently, Treska et al. (75) reported interesting results on the impact of endogenous fibrinolysis in patients with lower limb ischemia. The authors have measured the antigens of tPA and PAI, their related activity and tPA/PAI antigen and activity ratios in 420 patients, and they have shown increased levels as compared with healthy controls. There was a trend toward a higher values of tPA activity, tPA antigen, PAI antigen and tPA/PAI activity ratio in patients with critical leg ischemia as compared with severe claudication, and in patients with infrainguinal arterial disease as compared with those with aortoiliac disease, respectively.

Killewich et al. (88) reported a significant inverse correlation between the levels of tPA antigen and pain-free walking time in patients with claudication. Patients with severe claudication had significantly higher levels of tPA antigen compared with those with mild claudication.

Interestingly, Mustonen et al. (69) have shown that in claudicants submaximal physical exercise is associated with a significant increase in the levels of these parameters as well as in thrombin-antithrombin III complex as compared with controls. The authors concluded that strenuous exercise can be associated with increased risk in atherosclerotic patients probably because circulating platelets that come in contact with atherosclerotic arterial wall under pathological shear forces may be further activated by elevated catecholamines (69). This prothrombotic tendency is likely to lead to thrombotic complications after exertion in patients with severe atherosclerotic disease.

Killewich et al. (74) observed a significant increase in PAI-1 activity and decrease in tPA activity levels after infrainguinal bypass surgery, which returned to normal levels by 72 hours after surgery. This important observation suggest that postoperative anticoagulation may be useful to avoid immediate graft occlusion in the setting of such a temporary worsening in fibrinolytic activity during the immediate postoperative period.

Other studies have shown that fibrinogen, FDP, D-dimer and von Willebrand factor antigen (76) and hemorrheologic factors (89) failed to decrease to the levels of controls after treatment and resolution of critical limb ischemia. Kauhanen et al. (73) showed that upregulation of PAI-1 mRNA expression and increased amount of PAI-1 antigen were detected in failing vein grafts. These latter observations suggest that such derangements in fibrinolytic activity may occur at systemic and local level contributing to poor surgical and survival outcome after arterial revascularization.

Hyperhomocysteinemia

In 1969, McCully (90) brought the first evidences about the association between hyperhomocysteinemia and arterial thrombosis and atherosclerosis, and subsequent, extensive research has confirmed and clarified the impact of elevated homocysteine levels in the pathogenesis and progression of cerebrovascular (91-93), coronary (92,94,95), and lower limb artery disease (96,97). A recent study from the Framingham population showed that subjects with levels of homocysteine in the upper quartile had a significantly higher incidence of carotid stenosis (stenosis>25%, OR: 2) (98). Taylor et al. (97) showed that an increase in 1.0 micromol/L resulted in a 5.6% risk of death from cardiovascular disease (C.I. 95%, 2.2-8.5, p = 0.003).

There is evidence that hyperhomocysteinemia is particularly associated with the development of lower limb ischemia (97). Duan et al. (99) showed that hyperhomocysteinemia impairs the angiogenesis in an experimental model of limb ischemia. This finding suggests that patients with lower limb ischemia with increased levels of homocysteine may have poorer outcome due to impaired formation of collateral circulation.

Such a great interest in homocysteine is also related to the high incidence of hyperhomocysteinemia among patients with chronic renal failure (100), a patient-population who is at an extremely high risk for adverse cardiovascular events, and to the speculation that treatment with folate, vitamin B6 and B12 may improve the prognosis in patients with hyperhomocysteinemia (101).

Elevated plasma levels of homocysteine may result from inherited disorders of the transsulfuration and methylation pathways or from acquired deficiencies of

folate, vitamin B6 and B12, the latter accounting for 67% of cases of hyperhomocysteinemia in a recent Framingham population study (98). Homocysteine levels is measured as fasting homocysteine and after methionine loading test (100 mg/kg). Mild hyperhomocysteinemia has been reported in 29% of subject in the Framingham study, whereas severe hyperhomocysteinemia is much less common (98). Rauh et al. (102) did not find any case of mild hyperhomocysteinemia among children, and observed that men had a significantly higher incidence of mild hyperhomocysteinemia than women.

Oxygen radicals are produced by the oxidation of homocysteine resulting in endothelial damage, smooth muscle proliferation and activation of platelets and leukocytes, which are responsible for the development of premature, aggressive atherosclerosis (103).

Furthermore, increased plasma levels of homocysteine have been shown to result in a prothrombotic state secondary to enhanced activity of factors V and VII, decreased activation of protein C, inhibition of antithrombin binding activity of the endothelium produced heparan sulfate, and alteration in the binding of tissue plasminogen activator (103).

Several studies have shown that treatment with folate, vitamin B6 and vitamin B12 can effectively reduce homocysteine levels, and normalize platelet and endothelial cell function (101). Vitamin treatment has been shown to be less effective in patients with end-stage renal failure. Sepe et al. (104) reported a normalization of homocysteine levels in 19% of patients at 5-month follow-up after supplementation with folate, and vitamin B6 and B12, whereas a normalization (< 12 micromol/L) was observed in only 5% of hemodialysis treatment in the study by Bostom et al. (105). The authors observed a better response to vitamin treatment in renal transplant recipients (50% had normalization of homocysteine levels < 12 micromol/L, p = 0.002) (105).

Studies employing samples of the Framingham Study Offspring Cohort showed that folic acid fortification of flour and cereal grain products resulted in a significantly increase in the mean folate concentrations from 4.8 to 10.0 ng/mL (p<0.001) and prevalence of low folate (<3 ng/mL) decreased from 22.0 to 1.7% (P < 0.001) between the baseline and follow-up visits as compared with controls. Mean homocysteine concentration decreased from 10.1 to 9.4 microM (P < 0.001), and prevalence of high homocysteine (> 13 mumol/L) decreased from 18.7 to 9.8% (P < 0.001) between study visits. No significant changes were observed among controls (98).

Taylor et al. (97) reported the results of a prospective study in patients with carotid and lower limb artery disease who were evaluated for the presence of hyperhomocysteinemia (> 14 micromol/L). At 3-year follow-up, cardiovascular mortality was significantly higher in patients with hyperhomocysteinemia than in those with normal levels of homocysteinemia (12.5% vs. 6.3%, p = 0.05). The subjects in the highest 20% of plasma homocysteine values had a 3-year survival rate of 71% compared with 95% survival rate in those with the lowest 20% of homocysteine values (p = 0.0006). The progression of coronary artery disease was also significantly increased in hyperhomocysteinemic patients (p = 0.007). An evident, but not statistically, significant, increased progression was also observed in cerebrovascular and lower limb artery disease as well as in the rates of myocardial infarction, stroke and severe leg ischemia. However, the latter differences failed to reach statistical significance. Although this study brought strong evidence on the impact of increased levels of homocysteine and on the progression of peripheral and coronary artery disease, the results could be somewhat influenced by significantly higher levels of cholesterol, cotinine, and creatinine among hyperhomocysteinemics. However, multivariate analysis adjusted for these risk factors, showed that there is an increased risk of cardiovascular death of 5.6% for each increase of 1 micromol/ of homocysteine (97).

Hyperhomocysteinemia seems, therefore, to be an important cardiovascular risk factor which deserves further studies, in particular, to evaluate the real therapeutic impact of vitamin supplementation on the progression of atherosclerosis. Screening for hyperhomocysteinemia and interventional studies would be particularly justified for stratification and therapeutic modification of the risk of patients with CLI, since the latter seems to be significantly associated with increased levels of homocysteine (97).

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia is a rare acquired condition which may occur in less than 5% of patients undergoing heparin therapy. This condition is secondary to the production of heparin-associated antiplatelet antibodies which usually occur between the 5th and 8th day after exposure to any form of heparin. The development of these antibodies is independent of patient age, sex, the rout of administration and the amount of heparin received and it leads to activation and aggregation of platelets and, thus, to thrombosis or, only rarely, hemorrhage. However, the incidence of heparin-associated antiplatelet antibodies may be far beyond the incidence of clinically evident cases of thrombosis. In fact, Nand et al. (106) reported an incidence of 29% clinically complicated cases among 108 patients who had a diagnosis of heparin-induced thrombocytopenia. A decrease in platelet count may occur,

but it is not a constant finding. A test to detect the presence of heparin-associated antiplatelet antibodies should be done in all suspected cases. Suspicion of this condition should lead to discontinuation of heparin administration and aspirin, dextran 40, danaparoid, or lepirudin should be administered. Since positive reaction to low-molecular weight heparins is encountered in less 34%, when the patient with heparin-induced thrombocytopenia does not cross react to one of them, a brief exposure to that type of heparin, e.g. enoxaparin or dalteparin, has been also suggested with retesting for potentially new antibodies to the new type of heparin a few days later (103).

When promptly recognized and treated, this condition is associated with acceptable morbidity and mortality rates, being 7.4% and 1.1%, respectively in the series by Almeida et al. (107).

Antiphospholipid syndrome

This a relatively common acquired hypercoagulable condition occurring in up to 5% of the population (103), but the incidence may be up to 26% in patients undergoing vascular surgery (108) and even higher among the elderly (109). The development of lupus anticoagulants or anticardiolipin antibodies is responsible for this prothrombotic condition. These antibodies are directed against ß 2 glycoprotein I, prothrombin, protein C, protein S, factors XI and XII, high-molecular weight kininogen, and phospholipids of endothelial cells and platelets (103). Venous and arterial thromboses, the latter occurring in the coronary (110-112), cerebrovascular (113), peripheral (114) and eye (115) circulation, recurrent and mid-pregnancy abortion and thrombocytopenia are the common clinical manifestations of this disorder.

This condition is recognized as a strong risk factor for postoperative graft failure after arterial revascularization (108). Interestingly, Lam et al. (116) observed an association between the presence of antiphospholipid antibodies and the progression of lower limb artery atherosclerosis, which was significantly increased only in the superficial femoral, popliteal, anterior tibial and posterior tibial arteries and not in the iliac and common femoral arteries. Patients under oral anticoagulation tended to have a lessened progression of the disease compared with those not receiving anticoagulation (63% vs. 84%, p=0.06).

Aspirin and hydroxychloroquine can be useful in primary prevention (117), whereas anticoagulation is the recommended treatment in patients having had thrombotic events or severe atherosclerotic disease (108,117). Plasmapheresis with immunosuppression or intravenous administration of immunoglobulins showed promising results in the setting of catastrophic antiphospholipid syndrome (117).

Antithrombin III deficiency

Antithrombin III is an inhibitor of thrombin and of the coagulation factors IXa, Xa, XIa, and XIIa. Its deficiency, acquired or hereditary, may results in venous and arterial thrombosis (103). Thromboembolism is rare before the second decade of life, and surgery, trauma, sepsis, nephrotic syndrome, or pregnancy may trigger the development of such vascular complications. Levy et al. (87) reported an incidence of antihtrombin III deficiency in 10% of patients having premature lower extremity atherosclerosis, whereas Valentin et al. (118) did not find it as a risk factor of lower limb atherosclerosis in young patients. However, it has been recognized as risk factor for coronary (119) and cerebrovascular events (120), and bypass graft failure (121).

In case of thrombosis, heparin should be administered and antithrombin activity increased to more than 80% of normal activity employing fresh frozen plasma and antithrombin concentrates. Long-term oral anticoagulation should be administered in patients with thrombotic events. Relatives of patients with this disorder should be screened and, if found to have antithrombin deficiency, anticoagulation should be administered in case of surgery, trauma, sepsis, nephrotic syndrome or pregnancy.

Protein C and protein S deficiencies

Protein C and protein S are vitamin K-dependent proteins which are produced by the liver. Protein C is a potent anticoagulant and enhances fibrinolysis after having been activated by thrombin. Protein S has no anticoagulant or fibrinolytic activity but enhances the anticoagulant effect of protein C (103). Deficiencies of these proteins can be congenital or acquired. Patients with homozygous deficiency of protein C have often lethal thrombotic complications during early life, whereas patients with heterozygous deficiency of this protein may experience venous thrombotic events in up to 50% of cases (122).

Acquired deficiencies of protein C and S may occur in patients with hepatic failure, deficiency of vitamin K, chronic renal failure, disseminated intravascular coagulation and during active thrombosis (103).

Deficiencies of protein C and S is usually associated with venous thrombosis. However, cerebrovascular and lower limb ischemic events have been described, and the risk of vascular complications is increased by the coexistence of deficiency of both these protein (123). There is a particular predisposition for stroke in young patients, but, on the contrary, the impact of these prothrombotic states on myocardial infarction is controversial (124).

Eldrup-Jorgensen et al. (125) have reported an incidence of deficiency of protein C in 15% and of protein S in 20% of patients younger than 50 years undergoing revascularization for lower limb ischemia. Levy et al. (87) reported an incidence of deficiency of protein C in 23.1% of young patients with acute leg ischemia, 13.3% of patients with lower limb ischemia, and 38.1% of them had a previous vascular operation ($p<0.01$). Deficiency of protein S has been observed in 15.1% of patients with acute leg ischemia, 5.4% of patients with lower limb ischemia, but there was no difference between patients with and those without a previous vascular operation (87).

Life-long anticoagulation is indicated in patients who experienced thrombotic events.

Activated protein C resistance/factor V Leiden mutation

Activated protein C degrades the activated clotting factors VIII and V, but in this condition a mutation of in factor V is often present and prevents the degradation of factor Va (factor V Leiden) by activated protein C. The result is a prothrombotic tendency due to uncounteracted action of the clotting factor Va. However, a poor response to activated protein C without concomitant factor V Leiden mutation has been also recognized (126-129), especially among nonwhite populations. Activated protein C resistance is a relatively common prothrombotic disorder. In the heterozygous form, this condition is associated with a 7-fold risk of vein thrombosis which raises to 80-fold in the homozygous form (130,131). It is controversial whether activated protein C resistance/factor V Leiden mutation is associated with an increased risk for coronary events (70,132), but recently it has been shown that low response to activated protein C is a strong risk factor for advanced peripheral vascular disease (128), and a strong association with vascular dementia (RR, 4.28) (133) and stroke in young adults (134) has been reported.

Foley et al. (135) observed this prothrombotic disorder in 18% of patients with peripheral vascular disease undergoing arterial revascularization. Sampram et al. (129) detected a factor V Leiden mutation or and activated protein C ratio of 2.6 in 28% of patients peripheral vascular disease. Factor V Leiden mutation was seen in 15% of patients and abnormal activated protein C ratio in 20% of patients. Interestingly a significantly higher incidence of abnormal activated protein C ratio was observed among patients with femoropopliteal (33%, $p<0.001$) and aortoiliac occlusive disease (18%, $p<0.05$) as compared with the control group. However, such rates were also higher as compared with patients with other arterial disorders. Patients undergoing aortoiliac and femorocrural arterial reconstruction had an incidence of factor V Leiden gene mutation of 41% and 43%, respectively, and an abnormal activated protein C ratio of 35% and 46%, respectively that was significantly higher than in the control group ($p<0.001$). Among patients that experienced graft occlusion, factor V Leiden gene mutation ($p<0.001$) or abnormal activated protein C ratio ($p<0.001$) was detected in 32% and 49% of them, respectively.

Recently, the same authors (136) reported an higher incidence of graft occlusion after peripheral vascular surgery in patients with this conditions. Among patients who underwent infrainguinal bypass surgery, the 1-month and 12-month graft occlusion rates were 37% and 46%, respectively, in those with factor V-Leiden mutation, and 22% and 27%, respectively, in patients without this mutation (p=ns).

These observations suggest that insensitivity to activated protein C is a strong cardiovascular risk factor for the development of thrombotic events and advanced atherosclerosis. Further studies are, thus, required to evaluate the epidemiologic impact and to elucidate the mechanisms underlying this prothrombotic disorder.

Prothrombin gene variant (20210A)

Poort et al (137), in 1996, have discovered a mutation of the prothrombin gene leading to increased levels of prothrombin and resulting in increased risk for venous thrombosis. However, several studies reported controversial results on whether patients carrying this mutation are at increased risk of coronary and cerebrovascular complications. Controversial is also the issue whether this mutation is associated with development of peripheral arterial disease (138,139). Recently, Russo et al. (140) did not find any association between this prothrombin gene mutation and the occurrence of myocardial infarction, but the authors observed that high levels of prothrombin were significantly associated with the presence of coronary artery disease as detected by coronary angiography.

Smoking

Smoking habit is a well recognized risk factor for atherogenesis and arterial thrombosis. It may lead to a prothrombotic state through different mechanisms. In particular, smoking reduces the synthesis of prostacyclin, and increases blood viscosity, coagulation and platelet activation. Nicotine and carbon monoxide result in endothelial injury and permeability, respectively, which in turn results in platelet and lipid deposition, thus leading to pathogenesis of atherosclerotic lesions.

The recent results from the Rotterdam Study (84) showed that current smoking is the most significant risk factor for development of peripheral arterial disease as dia-

gnosed by and ABI<0.70 (OR, age- and sex-adjusted: 3.35; from multivariate analysis: OR 1.66).

A large study evaluating the effect of smoking on the outcome of myocardial infarction showed that smokers had significantly increased levels of fibrinogen, platelets and hematocrit compared with non-smokers (141). However, the smokers had significantly less extensive coronary artery disease as assessed by the larger diameter of the normal reference segment of the infarct vessel and the reduced incidence of three vessel-disease. Furthermore, in-hospital death, recurrent unstable ischemia, stroke and the need for urgent revascularization was significantly more frequent in smokers than in non-smokers. These observations suggest that smoking is likely to be associated with hypercoagulable state which may be responsible of thrombosis in presence of less critical atherosclerotic coronary lesions, thus it is likely more responsible to thrombolytic therapy.

The results from the Edinburgh Artery Study (83) confirmed the positive interaction between smoking habit and the level of fibrinogen, the latter correlating with the severity of lower limb ischemia as graded according to ABI.

Recently, Hioki et al. (142) provided evidence of platelet-dependent thrombogenesis among smokers. In fact, platelet-dependent thrombin levels were significantly higher among smokers compared with non-smokers, and that smoking of two cigarette resulted in transient three-fold increase of platelet-dependent thrombin level.

It has been shown that in women using contraceptives, smoking is associated with absence of compensatory fibrinolytic effects leading to a hypercoagulable state (143).

Furthermore, smoking has been shown to increase the risk of cardiovascular events in patients with other prothrombotic states such as resistance to activated protein C (144), deficiency of protein S (145), and increased activity of coagulation factor V (OR smoker vs. non-smokers in the highest quartile, 2.3) (70). Inbal et al. (146) have shown that the risk of myocardial infarction is 25-fold increased when current smoking is combined with prothrombotic and Apo E4 polimorphisms.

Finally, Bergmark et al. (96) showed that in patients below 50 years suffering lower limb ischemia, smoking was significantly associated with higher serum levels of homocysteinemia, a well known risk factor for aggressive atherosclerosis. In this study, smoking was associated with low levels of B6, which may explain such an increase of serum levels of homocysteine among smokers.

Other risk factors associated with hypercoagulable states

Diabetes, hyperlipidemia, myeloproliferative diseases, and thrombotic thrombocytopenia are also associated with an increased risk of thrombotic events due to their effects on platelet function (103).

Microalbuminuria

Several studies have shown that microalbuminuria is a relevant risk factor for the development of cardiovascular disease. The incidence of microalbuminuria is particularly increased in patients with diabetes, hypertension, smoking, and dyslipidemia, and it has been estimated to be 7.2% in the general population, being 6.6% among subjects without diabetes and hypertension (147). It is a useful marker of progressive renal insufficiency even in absence of increased serum levels of creatinine.

Microalbuminuria has been shown to be associated with increased risk of coronary artery disease among non diabetic patients (148), of myocardial ischemia and left ventricular hypertrophy among patients with essential hypertension (149,150), and of 1-year mortality after myocardial infarction (151).

Microalbuminuria was found to be associated with increased levels of von Willebrand factor, thrombomodulin, fibrinogen, thrombin–antithrombin III complexes and impaired fibrinolytic activity and may thus be a marker of a prothrombotic state (67,152-154). Furthermore, microalbuminuria has been associated with increased levels of C-reactive protein, which itself is associated with an increased risk of cardiovascular disease (155).

Jager et al. (156) reported a relative risk of 3.3 for cardiovascular mortality in patients with microalbuminuria, whereas it was 13-fold increased when microalbuminuria was associated with peripheral vascular disease as graded by an ABI<0.9 or previous lower limb revascularization or amputation.

Miettinen et al. (157) showed that urinary protein concentration has a significant impact on 7-year cardiovascular mortality and morbidity both in non-diabetics and non-insulin dependent diabetic patients. Patients were stratified in three categories: no proteinuria (<150 mg/L), borderline proteinuria (150 to 300 mg/L), and clinical proteinuria (>300 mg/L). Among the non-diabetics, the rates of late stroke according to these risk categories were 1.6%, 3.2%, and 8.5% ($p<0.001$), whereas among non-insulin dependent diabetics were 7.2%, 11.1% and 23.0% ($p<0.001$), respectively. The rates of fatal and nonfatal cardiac events were 3.4%, 6.4%, and 10.2% among non-diabetics ($p=0.02$), respectively, and 18.4%, 25.7%, and 34.8% among non-insulin dependent diabetics ($p<0.001$), respectively.

The risk of lower limb amputation among non-insulin dependent diabetics was also affected by the urinary protein concentration (3.9%, 5.7%, and 12.2%, respectively, according to the above mentioned categories, p=0.001)

As suggested by the results of the Gæde and colleagues' study (158), intensive treatment aiming to correct microalbuminuria and other associated risk factors in patients with type-2 diabetes can significantly slow the progression of nephropathy, retinopathy and peripheral neuropathy, and to reduce the incidence of adverse cardiovascular events. Although it is strongly associated with other cardiovascular risk factors and it is not clear whether is itself an independent cause of cardiovascular disease (159), microalbuminuria should be considered as an important marker indicating a distinct increased risk for the development of atherosclerosis and its complications.

Chronic renal failure

Chronic renal failure is a formidable risk factor for the development of aggressive atherosclerosis, and especially patients on long-term dialysis are at high risk for early myocardial infarction, congestive heart failure, stroke and CLI. It has been shown that cardiac mortality in dialysis patients younger than 45 years is more than 100 times greater than in the general population (135). However, despite a body of evidence on the adverse impact of impaired renal function on the development of cardiovascular diseases, there is still lack of knowledge about the factors resulting in aggressive atherosclerosis and, consequently, how to correct them in order to improve the long-term outcome. This may be due to difficulties to study sick populations such as the one with chronic renal failure, since the coexistence of different diseases may result as confounding, therefore, limiting the possibility to identify the true determinants of cardiovascular disease (159).

Kantonen et al. (160) in an analysis of 2296 surgical revascularization procedures for CLI showed that renal dysfunction was significantly associated with postoperative mortality (OR, 2.66), and the risk is even higher in patients on long-term dialysis (161). There are several studies indicating that the results after revascularization for CLI in patients on long-term dialysis are not brilliant (41,161-170), especially in those with low levels of serum albumin and coronary artery disease (162). Early and long-term survival outcome and leg salvage rates are of main concern. In a study evaluating the 30-day postoperative outcome of infrapopliteal bypass surgery, Biancari et al. (41) observed that dialysis was predictive of major postoperative amputation (OR: 4.88), major amputation with open graft (OR: 7.82), and death and/or amputation (OR: 4.42). Furthermore, the same authors reported a 2-year survival rate of 23%, being 0% among patients with coronary artery disease (p=0.006) after lower limb revascularization for CLI in patients on long-term dialysis. Similar poor results have been reported by other authors as well, only a few patients on long-term dialysis with CLI surviving beyond the third postoperative year (162,163-166,168-170). A few studies reported better results in terms of leg salvage and survival rates (171-174), however, different results in this high risk patient population may reflect differences in the selection of patients undergoing lower limb revascularization.

Herein, we briefly describe the cardiovascular risk factors associated with chronic renal failure. Patients with renal failure are often hypertensive probably as a result of plasma volume expansion, sodium retention, impaired renal autoregulation, overactivity of the sympathetic nervous system and the renin-angiotensin-aldosterone system, the accumulation of endogenous vasoactive substances, and the use of erythropoietin (175,176,177). If left untreated, hypertension may further aggravate the glomerular filtration rate, thus resulting in further renal damage. Hypertension is also responsible of left ventricular hypertrophy, and it is linearly associated with the risk of coronary artery disease, congestive renal failure and stroke (178).

Dyslipidemia has been recognized as a major risk factor for the development of atherosclerosis in patient with chronic renal failure (179). In fact, dyslipidemia not only may cause a further decline in renal function (180), but it is significantly associated with development of atherosclerotic lesions and arterial calcification in patients on long-term dialysis (181). It seems that also patients with kidney transplant suffer of dyslipidemia in more than 70% of cases (182). Increased concentrations of LDL, with a predominance of small dense LDL, lipoprotein (a) and other lipoproteins, and low concentrations of HDL-cholesterol are typically found in this patient population, requiring aggressive lipid-lowering diet and therapy (183).

Decreased glomerular-filtration rate has been shown to be associated with increased levels of plasma total homocysteine, which, as extensively discussed in the paragraph dealing with prothrombotic states, is known as an independent cardiovascular risk factor.

Chronic renal failure are usually associated with alterations in the concentrations of acute-phase reactants like increased concentrations of fibrinogen and C-reactive protein and hypoalbuminemia, which are recognized as risk factors for adverse cardiovascular events. In particular, hypoalbuminemia is a strong determinant of mortality in dialysis patients. In a study

by Owen et al. (184), the odds ratio for death in patients undergoing hemodialysis was 1.48 for serum albumin concentration of 3.5 to 3.9 g/dl, 3.13 for concentration of 3.0 to 3.4 g/dl, and 7.08 for concentrations of 2.5 to 2.9 g/dl. A significant negative impact of hypoalbuminemia on the survival outcome of patients on long-term dialysis with CLI has been observed as well (162).

Aberrations in calcium and phosphorus metabolism may cause accelerated atherosclerosis by deposition of calcium in vessels and soft tissues. Cardiac and vascular surgeons know this phenomenon called calciphilaxis well, because it results in circumferential calcification of the arteries and causes not a few problems when surgeon performs an arterial anastomosis on these porcelain vessels (185). This process of arterial calcification seems to correlated with the age of the patients, the duration of dialysis, the mean serum phosphorus concentration, the mean serum calcium-phosphorus ion product and the intake of calcium (186).

Conclusions

The "graying" population of the Western countries calls for increasing burden of vascular surgery activity. This phenomenon parallels with a constant increase of the comorbidities associated with lower limb ischemia (187), and requires a more careful evaluation and aggressive treatment of cardiovascular risk factors to improve the immediate and long-term outcome of these patients. This should lead vascular surgeons to treat patients with CLI in an integrated fashion in order improve the results of lower limb revascularization, which can not be measured only in terms of graft patency and leg salvage rates.

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