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HIV-occlusive vascular disease

J. VAN MARLE, M.B. CH.B., M.MED. (CHIR.), F.C.S. (S.A.)
P. P. MISTRY, M.B. CH.B., M.MED. (CHIR.), F.C.S. (S.A.)
K. BOTES, M.B. CH.B., M.MED. (CHIR.), C.V.S. (S.A.)
MediClinic Unit for Peripheral Vascular Surgery, Pretoria Academic Hospital, University of Pretoria

Abstract

Objectives. To evaluate peripheral arterial occlusive disease in HIV-infected patients regarding clinical presentation and outcome of surgical intervention.

Design. Prospective clinical survey.

Patients and methods. Routine voluntary testing for HIV/AIDS was performed in all patients presenting to our vascular unit. HIV+ patients were enrolled in a registry and followed up prospectively.

Results. We identified 154 HIV+ patients, of whom 91 (59%) presented with occlusive disease. There were 71 males and 20 females with a mean age of 44.2 years. The usual risk factors for atherosclerosis were present, but the incidence was less than reported in the classic atherosclerosis population. More than 90% of the patients presented with advanced stage vascular disease (Fontaine III/IV), which explains the high rate (31.9%) of primary amputation. Eighty-seven patients presented with lower-limb ischaemia, 2 patients with upper-limb ischaemia and 2 patients with symptomatic carotid artery stenosis. Seventy-eight procedures were performed on 72 patients, with a perioperative mortality of 6.95%. The limb salvage rate for femoro-popliteal bypass procedures was poor (36.1%), resulting in a high incidence of secondary amputations and prolonged hospital stay. Long-term mortality for the operated patients was 20% over a mean follow-up period of 15.4 months. Hypo-albuminaemia was found to be an important predictor of outcome.

Conclusion. Patients presenting with HIV-associated peripheral arterial disease should be carefully selected for intervention, taking into consideration nutritional and immune status, stage of the vascular disease and selecting the appropriate procedure.

The incidence of patients infected with human immunodeficiency virus (HIV) or suffering from acquired immunodeficiency syndrome (AIDS) is still increasing. This is due to not only the number of new infections, but also because highly active antiretroviral therapy (HAART) has significantly reduced the risk of early death from opportunistic infections. More than 85% of the HIV-infected population survive more than 10 years and most young patients with HIV infection can expect a survival of more than 30 years owing to HAART.[1,2]

There is a well-documented relationship between vascular disease and HIV infection.[3-6] Epidemiological studies have reported a high prevalence of cardiovascular disease among the young HIV-infected population.[7,8] Vascular surgeons must therefore be prepared to manage an increasing number of patients with HIV-related vascular diseases. We started a prospective clinical audit of patients presenting with HIV-related vascular disease in 2000 and have since reported our initial findings as well as 5-year follow-up.[9,10] This report describes our experience with HIV-related occlusive disease.

Patients and methods

Since January 2001 we followed a programme of routine voluntary testing for HIV/AIDS in all patients admitted to our vascular unit. The routine work-up for patients presenting with arterial disease was performed on all patients, including comprehensive screening for the accepted risk factors for atherosclerosis. Additional tests in HIV-positive patients included CD4 and CD8 T-cell counts, viral load, and screening for sexually transmitted infections. During the early phases of our study hypercoagulability screening was performed on all patients. The positive yield, however, was low and in the interest of cost containment routine hypercoagulability testing was discontinued. All patients received arterial duplex Doppler scans with either CT angiography or digital subtraction angiography as further imaging.

As no specific guidelines were available at the time, we based our elective management on the immune status, relying on the CD4 T-lymphocyte counts. Patients with a CD4 T-cell count of ≥500 cells/μl were managed according to standard vascular protocols as applied in seronegative patients. In patients with a CD4 T-cell count of between 200 and 499 cells/μl a conservative alternative to surgery was applied if possible. Where surgery was unavoidable, a less invasive procedure was chosen, e.g. endarterectomy ± profundoplasty or an extra-anatomical bypass procedure such as an axillo-femoral or femoro-femoral bypass rather than an aorto-bifemoral procedure. In patients with established AIDS (CD4 T-cell count <200 cells/μl) palliative treatment was administered, unless critical limb ischaemia necessitated intervention, which often meant primary amputation.

Standard surgical techniques were used. We have only recently started with endovascular treatment of suitable lesions in these patients. In HIV-infected non-AIDS patients we used standard prophylaxis as for all our vascular patients (cefazolin 2 g preoperatively), but in AIDS patients we used a broad-spectrum antibiotic as prophylaxis and continued with co-trimoxazole for 6 weeks, unless a positive culture and sensitivity dictated differently. A single dose of fluconazole as

prophylaxis against fungal infection was also routinely given in AIDS patients. Postoperative complications were documented. Only 4 of our patients were on antiretroviral therapy at initial presentation. Patients qualifying for HAART were referred to the relevant clinics at the time of discharge.

Results

We identified 154 HIV-positive patients as part of our routine screening programme. This constitutes 2.6% of all the patients that have given informed consent for HIV testing. Ninety-one patients (59%) presented with occlusive arterial disease. There were 71 male patients and 20 female patients, with a mean age of 44.2 years. The large majority of these patients were black (89%).

A significant number (39%) of our patients had AIDS with a CD4 T-cell count of <200 cells/µl ± other AIDS-defining conditions. Only 13.5% of the patients had CD4 T-cell counts of >500 cells/µl while 47.5% of the patients had CD4 T-cell counts of between 200 and 499 cells/µl.

Most patients presented with advanced vascular disease (Fig.1). Fifty-two patients (57.1%) presented with ulceration and gangrene (Fontaine IV, Rutherford category 5/6), 30 patients (33%) presented with rest pain (Fontaine III, Rutherford category 4) and 9 patients (9.9%) presented with short-distance claudication (Fontaine IIB, Rutherford category 3). The standard risk factors for vascular disease were identified. Seventy-two patients (79%) were smokers and 17 patients (18.7%) were hypertensive. There were only 5 diabetic patients (5.5%) and 2 patients with hypercholesterolaemia (2.2%). The only other significant finding was hypoalbuminaemia with a mean serum albumin of 24.4 g/l. Five patients presented with concomitant opportunistic infections.

Disease distribution is given in Table I. The majority of patients (46) presented with infra-inguinal disease and 21 had aorta-iliac occlusive disease. Although we have had a number of carotid artery aneurysms, we have seen only 2 patients with symptomatic carotid artery occlusive disease. A number of patients (14) presented with distal (infra-popliteal and pedal) disease, with 2 patients presenting with palpable pedal pulses, a normal ABI and digital gangrene. These patients had AIDS with a CD4 T-cell count of less than 50 cells/µl and concomitant cytomegaloviral infection (Fig. 2). The majority of our patients had characteristic angiogram findings of long segmental occlusions with poor or absent distal runoff (Rutherford angiographic score = 3). The proximal vessels were remarkably free of disease (Fig. 3a, b, c).

After evaluation of the patients' general condition and severity of disease, 81 patients were offered surgery and 10 patients were managed conservatively with best medical treatment. Nine patients refused surgery. Seventy-two patients underwent 78 procedures, which included surgical revascularisation in 44 patients and primary amputation in 23 patients. Sympathectomies were performed together

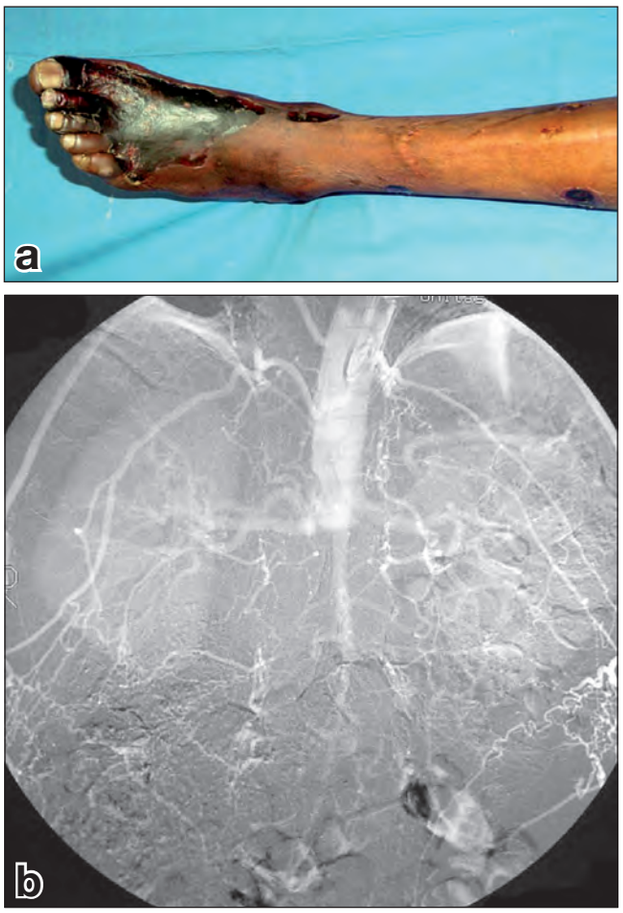

Fig. 1. Patient presenting with advanced vascular disease (Fontaine IV, Rutherford category 6) (a), due to occlusion of the abdominal aorta (b).

TABLE I. DISTRIBUTION OF ARTERIAL OCCLUSIVE DISEASE IN 91 HIV-INFECTED PATIENTS

Disease distribution	Number
Aorta-iliac	**21**
Ilio-femoral	**4**
Femoro-popliteal	**32**
Distal	**14**
Multilevel	**16**
Upper limb	**2**
Carotid	**2**

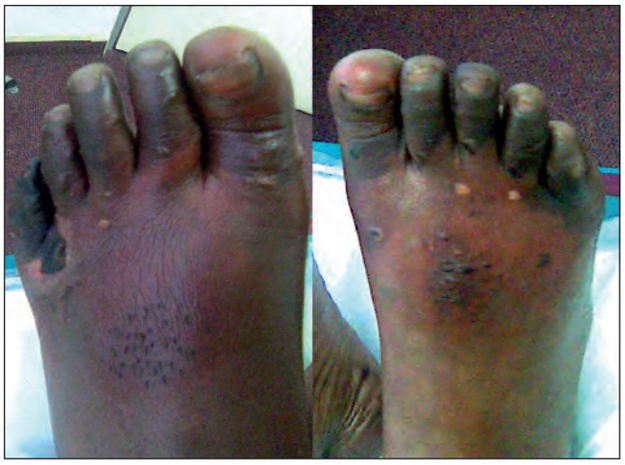

Fig. 2. A 28-year-old patient who presented with spontaneous digital gangrene in the presence of palpable pedal pulses. The CD4 T-cell count was 50 cells/µl and she was CMV positive.

with wound debridement or limited amputation of digits in 5 patients who were not amenable to bypass surgery. Four patients received endovascular treatment which consisted of catheter-directed thrombolysis followed by percutaneous transluminal angioplasty (3) and stenting (1) (Fig. 3 d, e). Two patients underwent carotid endarterectomy for symptomatic carotid artery stenosis without any complications. The perioperative mortality was 6.95% (5/72). The long-term mortality for the operated group was 23.1% (15/65; 7 patients were lost to follow-up) over a mean follow-up of 15.4 months. The long-term mortality for the whole group was 28.75% (23/80; 11 patients being lost to follow-up) over a mean follow-up period of 17.5 months. A list of the procedures and outcome is given in Table II.

There were 8 documented graft occlusions from 26 bypass procedures (30.8% occlusion rate). All the patients with occluded grafts were smokers, the mean CD4 T-cell count was 271 cells/µl and albumin 31 g/l for this subgroup. Post-surgical infections and sepsis occurred in 20 patients (27.8%). The mean CD4 T-cell count was 343 cells/µl. The most common organisms identified were α-haemolytic *Streptococcus* (wound), *Staphylococcus*, *Proteus mirabilis* (wound), *Cryptococcus* (CSF) and *Salmonella* (serum).

There was a significant correlation between serum albumin levels and poor outcome. The mean serum albumin concentration in patients who died postoperatively or within 2 years after surgery was 19 g/l and 20 g/l, respectively. The albumin concentration in patients who developed postoperative septic complications was 20 g/l. Haematocrit and total white cell count did not seem to influence postoperative outcome. CD4 T-cell count in survivors was 301 cells/µl compared with 252 cells/µl in those patients who died perioperatively or within 2 years. Due to the small sample size this does not reach statistical significance.

Discussion

There have been many reports on HIV/AIDS-associated vasculopathy since its first description in 1987, but relatively few have dealt with peripheral arterial occlusive disease.[9,11-13] Peripheral arterial disease (PAD) is more prevalent in the HIV-infected population than in the general population. A study by Periard *et al*. reported a six-fold increased risk for PAD in HIV-infected individuals as well as an earlier onset of the disease compared with HIV-negative patients.[13] Multivaried analysis in this study identified age, smoking, diabetes and CD4 T-cell count < 200 cells/µl as significant predictors of PAD. They also found no significant correlation with antiretroviral therapy. Depairon *et al*. found that 55% of HIV-infected patients had at least one carotid or femoral plaque compared with 38% of healthy controls.[14] Kaplan *et al*. reported a 70 - 100% increase in the prevalence of carotid artery lesions among HIV-infected individuals with a CD4 T-cell count <200 cells/µl compared with uninfected individuals.[15] Arterial stiffness is considered as an early monitor for atherosclerosis. Increased aortic stiffness, as determined by

TABLE II. PROCEDURES PERFORMED FOR LOWER-LIMB ISCHAEMIA

Procedure	Procedures (*N*)	30-day mortality	Sepsis	Occlusion	Amputation	Long-term mortality	Follow-up period (months)
Aorta-bifemoral bypass	**2**	**0**	**0**	**0**	**0**	**0**	**6**
Axilo-bifemoral bypass	**5**	**1**	**1**	**1**	**1**	**1**	**11.4**
Femoro-femoral bypass	**5**	**0**	**3**	**2**	**2**	**1**	**16.4**
Thrombendarterectomy with profundoplasty	**18**	**1**	**4**	**3**	**3**	**2**	**11.6**
Femoro-popliteal bypass (below knee)	**13**	**2**	**5**	**4**	**8**	**2**	**18.5**
Femoro-distal bypass	**1**	**0**	**1**	**1**	**1**	**1**	**3**
Endovascular	**4**	**0**	**0**	**0**	**0**	**0**	**4**
Primary amputation	**23**	**1**	**6**	**-**	**-**	**3**	**12.5**
Sympathectomy	**5**	**0**	**0**	**-**	**1**	**LTFU**	**LTFU**

*LTFU = lost to follow-up

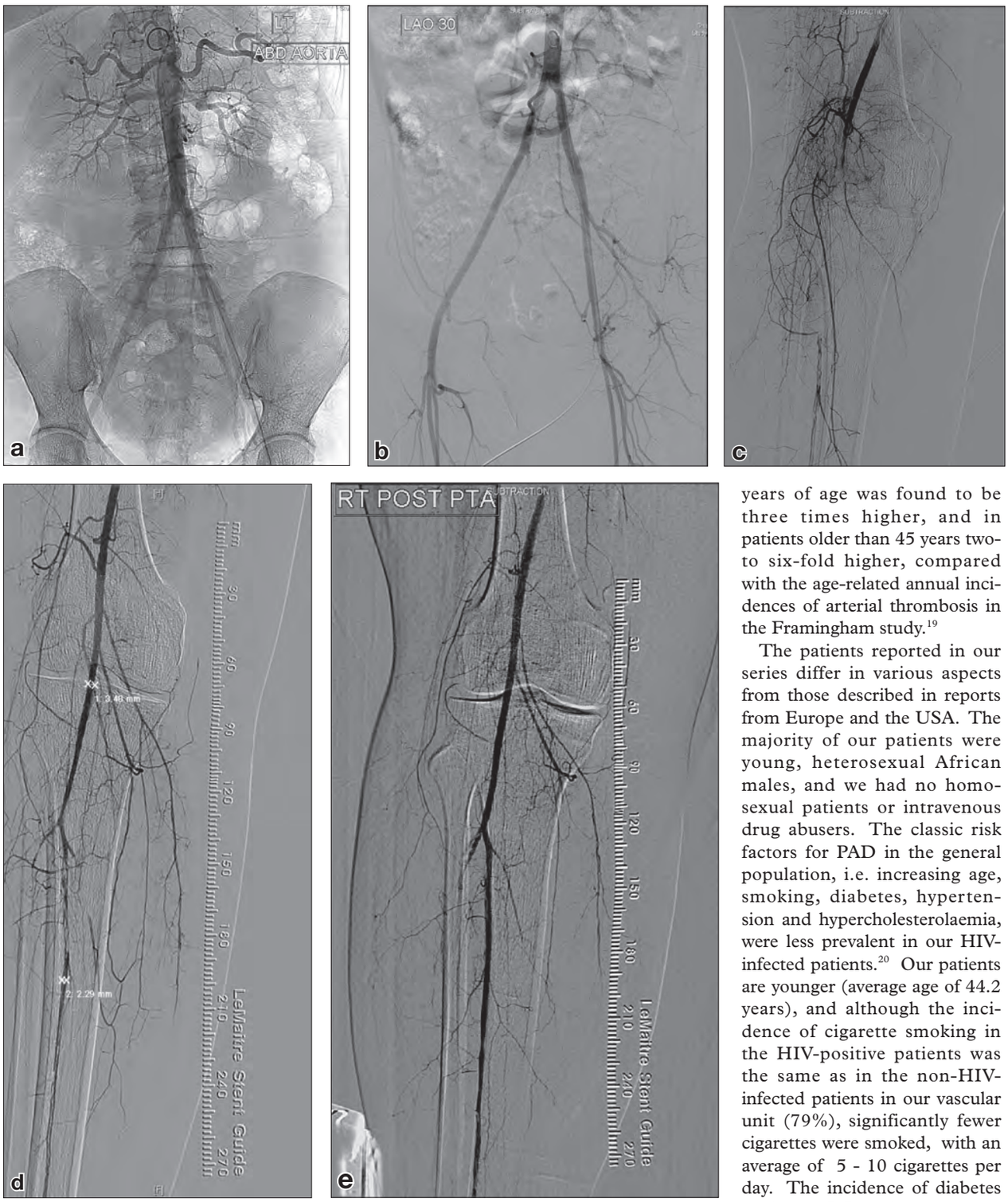

Fig. 3. Arteriogram of a 33-year-old female patient who presented with acute-on-chronic critical lower-limb ischaemia showing relatively normal proximal vessels (a and b) with severe distal disease and poor runoff (c). Catheter-directed thrombolysis was performed (d) followed by PTA (e).

aortic pulse wave velocity, and increased brachial artery stiffness, as measured by decreased flow-mediated dilation, have been observed in HIV-infected patients.[16-18] The risk of arterial thrombosis in HIV-positive patients younger than 45 years of age was found to be three times higher, and in patients older than 45 years two- to six-fold higher, compared with the age-related annual incidences of arterial thrombosis in the Framingham study.[19]

The patients reported in our series differ in various aspects from those described in reports from Europe and the USA. The majority of our patients were young, heterosexual African males, and we had no homosexual patients or intravenous drug abusers. The classic risk factors for PAD in the general population, i.e. increasing age, smoking, diabetes, hypertension and hypercholesterolaemia, were less prevalent in our HIV-infected patients.[20] Our patients are younger (average age of 44.2 years), and although the incidence of cigarette smoking in the HIV-positive patients was the same as in the non-HIV-infected patients in our vascular unit (79%), significantly fewer cigarettes were smoked, with an average of 5 - 10 cigarettes per day. The incidence of diabetes mellitus (5.5%), hypertension (18.7%) and hypercholesterolaemia (2%) is also significantly less than reported in the classic atherosclerosis patient population. HAART has been implicated in the premature onset of atherosclerosis, but only 4 patients in our series were on HAART at their initial presentation. HAART only recently became available to our patients; 5 patients are currently

receiving antiretroviral treatment, with a marked reduction in viral load and significant improvement in CD4 T-cell counts. One of these patients has been seen during follow-up with progressive disease requiring further management (thrombendarterectomy and profundoplasty).

Almost a third of our patients presented at a late stage with very advanced arterial disease and required primary amputations. Thirty-three patients were not considered for revascularisation surgery, either because the disease was not amenable to bypass (23 primary amputations) or the patient had advanced AIDS without limb-threatening ischaemia.[10] The rest of the patients who were considered for surgery were managed according to normal standard surgical protocols. Two aorta-bifemoral bypasses were performed on patients with a CD4 T-cell count >500 cells/µl. A midline transperitoneal approach was used and the bypass performed with polyester bifurcated prostheses with an end-to-end proximal anastomosis. There were no perioperative deaths or complications. Ten patients with aorta-iliac occlusive disease required extra-anatomical bypass procedures due to advanced disease (CD4 T-cell count <500 cells/µl) or poor respiratory function which contraindicated laparotomy. Five axillo-bifemoral bypasses and 5 femoro-femoral bypass procedures were performed using polyester (*N*=8) and PTFE (*N*=2) grafts. Silver-impregnated grafts were used where there was a high probability of infection. The extra-anatomical bypasses overall had a high incidence of wound complications (40%) with wound breakdown and graft sepsis resulting in graft removal and subsequent amputations in 3 patients.

Fourteen patients required femoro-popliteal bypass procedures. Autogenous vein was the preferred conduit (*N*=12) and PTFE only used in 2 patients where no vein was available due to diffuse thrombophlebitis. A characteristic feature in patients with infra-inguinal disease was the fibro-obliterative nature of the occlusion with cords/strings of fibrous tissue being removed from the arterial lumen (Fig. 4 a,b). There was an absence of classic atherosclerotic plaque which could be removed with endarterectomy. There was a high incidence of skin breakdown and subsequent wound infection over the area where the vein was harvested. Two patients died within 30 days and 9 patients required secondary amputation, ranging from 7 days to 6 months after the initial procedure, due to graft occlusion or uncontrolled sepsis. Patients who underwent secondary amputation after failed bypass surgery required a higher level of amputation and had a higher complication rate, resulting in longer periods of hospitalisation compared with patients who received primary amputations.

Thrombectomy or thromb-endarterectomy with profundoplasty was performed in 18 patients, with septic complications occurring in 4 patients and occlusions in 5 patients, requiring secondary amputations in 3.

The overall limb salvage rate for infra-inguinal disease was poor (52.8%) with only 19 patients out of 36 being alive with intact limbs after a mean period of 13.2 months.

We have limited experience with the endovascular management of HIV-associated vascular disease (3 endovascular aneurysm repairs and 4 patients with occlusive disease). The short- to medium-term results, however, are good and the minimally invasive nature of these procedures warrant further investigation.

Histological examination of arterial specimens showed chronic inflammation and other features indicative of an underlying vasculitic process in the absence of classic features of atherosclerotic plaque. Chetty *et al*. proposed that occlusive disease occurs secondary to the same leukocytoclastic vasculitis of the vaso vasorum that causes large-vessel aneurysm disease, i.e. a bipolar clinical expression of the same pathological process.[6]

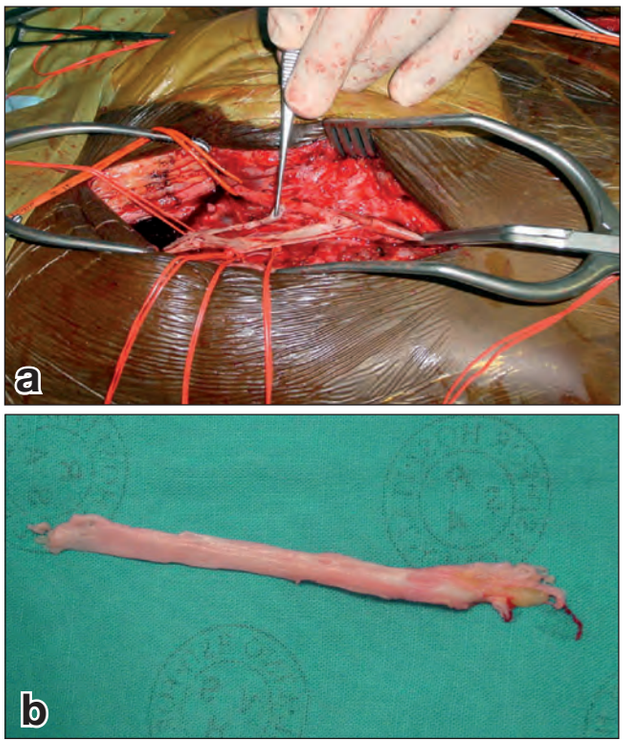

Fig. 4. Thrombendarterectomy of a common femoral artery (a) removing a fibrous cord from the lumen (b).

Perioperative mortality for all procedures was 6.95%. Eighty patients were available for follow-up, with a late mortality of 28.75%. Various factors influence the operative outcome of surgery in HIV-positive patients including immune status, opportunistic infections, white cell count, haematocrit, nutritional state (decreased albumin) and type of operation, i.e. emergency versus elective and clean versus contaminated surgery. Various authors have identified a CD4 T-cell count of <200 cells/µl as an important risk factor for postoperative complications.[12,22,23] There are, however, also studies that found no direct relation between CD4 lymphocyte counts and surgical infection or overall morbidity.[24] In our study there was a trend towards better survival in patients with a higher CD4 T-cell count (301 cells/µl in survivors versus 252 cells/µl in patients who died within 2 years). There was also no significant relationship in our patients between CD4 lymphocyte count and postoperative complications.

Lin *et al.*, in a multivaried analysis, showed that CD4 T-cell counts <200 cells/µl and hypo-albuminaemia (<35 g/l) were risk factors for postoperative complications ($p<0.05$).[12] Similar findings were reported by Binderow *et al.* and Bonarek *et al.*[25,26] Feldman *et al.* found that patients with serum albumin levels less than 35 g/l had a four-fold increased risk of death compared with those with normal albumin.[27] Almost 50% of the patients with hypo-albuminaemia died within 3 years compared with 11% of patients who had normal albumin levels. The researchers also reported that hypo-albuminaemia was a better predictor of mortality

in patients with CD4 T-cell counts >200 cells/µl and postulated that serum albumin may be a reliable predictor of outcome in the earlier stages of HIV infection. We similarly found an adverse relationship between low serum albumin, perioperative complications and long-term survival.

Low preoperative white cell counts, anaemia, the presence of opportunistic infections and clean versus contaminated surgery have also been shown to adversely affect the outcome of surgery.[21,25,28,29]

Savoiz *et al*. have shown that 35% of infective complications in HIV/AIDS patients are caused by opportunistic infections outside the range of normal vascular prophylaxis.[21] These, therefore, require therapeutic antibiotic and antifungal treatments according to microscopy, culture and sensitivity. We had a 27.8% incidence of wound infections, which is in accordance with other publications.

The increased incidence of peripheral arterial disease in HIV-infected persons could be explained in various ways:

HAART

Combination antiretroviral therapy has certain well-known metabolic side-effects (dyslipidaemia, insulin resistance, diabetes mellitus, lipodystrophy, metabolic syndrome, etc.) that may be associated with the premature development of atherosclerosis.[14,30] HIV infection and a low CD4 T-cell count have, however, been shown to be independent risk factors for atherosclerotic disease independent from HAART.[15,31,32] Furthermore, in the SMART study, cessation or interruption of antiretroviral treatment was associated with an increased incidence of major cardiovascular events.[33]

Hypercoagulabitily

Various abnormalities predisposing to a hypercoagulable state have been detected in HIV patients, including antiphospholipid antibodies, lupus anticoagulant, increased von Willebrand factor, deficiency in protein C and S, antithrombin and heparin co-factor. Viral-induced endothelial injury causes increased levels of von Willebrand factor, total antigenic protein S, plasminogen activator inhibitor (PAI-1), endothelial-derived thrombomodulin and other procoagulant products of endothelial cell activation.[34] Various other factors present in the AIDS patient, including opportunistic infections, neoplasms, antiretroviral therapy, etc. may also contribute to the hypercoagulable state. From the available literature, however, it appears that the thrombotic events are venous in nature and more common in patients with a CD4 T-cell counts <200 cells/µl. Skin necrosis and digital infarcts have been described in HIV-positive patients with positive antiphospholipid and lupus anticoagulant antibodies as well as cytomegalovirus infection (Fig 1).[35] There is also evidence of ultrastructural changes in thrombocytes with procoagulant microvesicles being released from apoptotic platelets, resulting in dynamic hypercoagulability as exposed on TEG examination.[36-38]

HIV-related injury to the arterial wall

Pathogenetic research supports the direct role of HIV in the development of arteriosclerosis. Endothelial dysfunction is a key step in the development of atherosclerosis and is known to be an early predictor of cardiovascular events.[39] Increased levels of soluble cellular adhesion molecules (VCAM-1 and ECAM), E-selectin as well as other markers of endothelial activation including von Willebrand factor, PAI-1 and tissue-derived plasminogen activator (tPa) suggest that the human immunodeficiency virus activates and disregulates endothelial cells. The exact mechanism of how the HIV causes endothelial cell dysfunction falls beyond the scope of this paper, and the reader is referred to some excellent review articles covering this topic.[40,41] HIV immunomodulation may also play a role as low levels of CD4 T-cells have been shown to be independent risk factors for the development of atherosclerosis.[13,15] The association between infection, inflammation and atherosclerosis is well known.[42] This suggests a causal relationship between the chronic inflammatory response caused by HIV as well as opportunistic infections such as cytomegalovirus and accelerated atherosclerosis.

Eugenin *et al*. demonstrated that human arterial smooth-muscle cells (SMC) can be infected *in vitro* and *in vivo* with HIV, resulting in a marked increase in SMC secretion of chemokine CCL2/MCP-1 which has been shown to be a critical mediator of atherosclerosis. Their data suggest that direct infection of human arterial SMCs by HIV may be an additional factor to endothelial cell dysfunction in the development of atherosclerosis and the vasculopathy seen in HIV-infected individuals.[43]

Conclusions

There is an increased incidence of peripheral arterial disease in the HIV-infected population. Although the precise mechanism is still unclear, the human immunodeficiency virus is directly implicated in the accelerated atherosclerosis in these patients.

The majority of our patients presented with advanced disease, which explains the high rate of primary amputations. A variety of surgical procedures were performed, with low perioperative mortality but a disappointing limb salvage rate, especially for fem-pop bypass procedures. The complication rate and duration of hospitalisation was also higher in patients who underwent secondary amputation for failed bypass surgery. Primary amputation is therefore an option to consider in patients presenting with advanced disease. There are many factors that influence perioperative outcome and long-term prognosis, of which CD4 T-cell count and hypoalbuminaemia seem to be the most important.

Patients should be carefully selected for intervention, reserving surgery for those with critical limb ischaemia, and opting for lesser invasive procedures, especially in patients with decreased CD4 T-cell counts. Early results of endovascular management in these patients are promising. Nutritional and immune status should be improved before intervention where possible. We hope that the increased availability of HAART will positively reflect on our future results.

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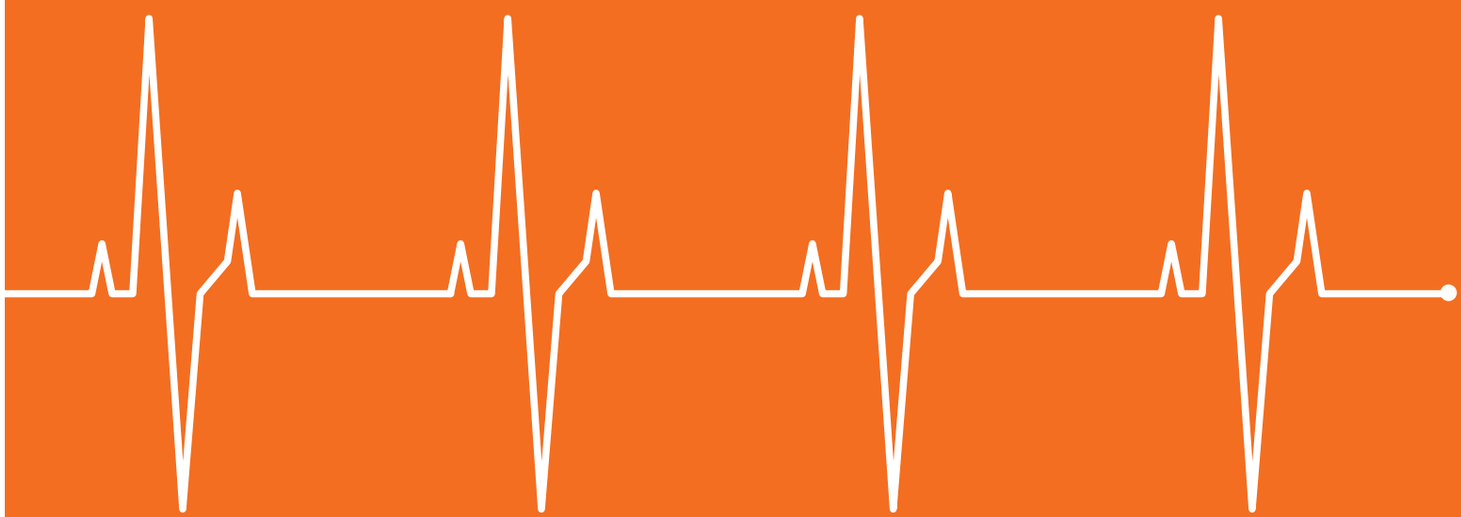

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