



Přehledový článek | Review article

Endovascular management of patients with peripheral vascular disease with cardiovascular multi-morbidity

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U pacientů s ischemickou chorobou dolních končetin se lze často setkat s postižením i jiných částí oběhové soustavy. Kardiovaskulární zátěž u těchto pacientů vyžaduje používání minimálně invazivních léčebných metod. Pokrok v technických možnostech u endovaskulárních výkonů a přibývající zkušenosti v posledních desetiletích přinesly alternativní řešení ke klasickým operacím. Tento přehled se zabývá kardiovaskulární morbiditou u pacientů s ischemickou chorobou dolních končetin, u nichž se současně provádí léčba pomocí endoskopických metod.

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ABSTRACT

Polyvascular presentation among patients with peripheral artery disease is common. The cardiovascular burden among those patients highlights the need of minimally invasive therapeutic techniques. Advances in endovascular technology and skills over the last decades offer an alternative to open surgery. This review discusses the cardiovascular morbidity in patients with peripheral artery disease and currently utilized endovascular management.

Introduction

The global prevalence of peripheral artery disease (PAD) increased significantly over the past decades; it affected approximately 202 million people worldwide in 2010 [1]. PAD is found to be associated with poor quality of life, cardiovascular morbidity and mortality especially for patients with PAD and pan-vascular disease [2]. The cardiovascular burden in patients with PAD highlights the need of minimally invasive therapeutic techniques. Previous studies demonstrated that patients with PAD had approximately a 5–7 fold increased risk of mortality from cardiovascular disease compared with patient without PAD [3–6].

Advances in endovascular technology and interventional therapy over the last decades offer an alternative to open surgery in many patients with cardiovascular co-morbidities with reported equivalent efficacy, lower peri-procedural risk and satisfactory late outcomes [7,8].

Mortality and cardiovascular morbidity in patients with PAD

The annual rate of cardiovascular events increases significantly in patients suffering from PAD [3–6]. Consequent-

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ly, cardiovascular events are the major cause of death among those patients. A long-term follow-up of 16,440 index patients showed that the annual mortality among patients diagnosed with PAD is higher than among patients with previous myocardial infarction (8,2% and 6,3%, respectively) [9]. Epidemiological data confirm that PAD is undertreated, thus contributing to the increased incidence of cardiovascular events [10].

Coexistence of PAD and coronary artery disease

There is considerable overlap between coronary, and peripheral atherosclerotic disease. Previous studies demonstrated that 22–42% of patients with coronary artery disease (CAD) have coexisting PAD [11–13]. The coexistence of PAD in patients with CAD is associated with worse prognosis [14]. Similarly coronary artery disease is common in patients with PAD. CAD was present in 58–68% of PAD patients [15,16]. According to the REACH-Register, patients with CAD and PAD are at increased risk for one-year fatal and non fatal cardiac events compared to patients with CAD [17]. The correlation between PAD and cardiovascular disease emphasizes the fact that PAD is a marker for pan-vascular disease.

Coexistence of PAD and heart failure

Heart failure is accompanied with low cardiac output and consequently reduced peripheral perfusion. Furthermore, coexistence of heart failure (EF <35%) impeded an expected improvement by supervised exercise program due to restricted physical activity [18]. A multivariate analysis of CORONA-trial showed an increased risk of mortality and myocardial infarction among patients with systolic heart failure and PAD [19]. Patient with heart failure should be therefore routinely screened for PAD.

Coexistence of PAD and cerebrovascular disease

A meta-analysis which enrolled 19 prospective studies including 45,738 patients showed a prevalence of 25% and 14% for >50% carotid stenosis and >70% carotid stenosis in patients with PAD, respectively [20]. Moreover, patients with PAD are at increased risk of cerebrovascular events. In a meta-analysis of 10 studies including 22,355 patients, PAD indentified by ABI <0.9 was associated with increasing risk of subsequent stroke and ischemic stroke (+43% and +83%, respectively) [21].

Likewise, PAD is common in patients with cerebrovascular disease (CVD) and has been reported in 44.9–

52% in patients with stroke or transient ischemic attack (TIA), especially when ankle brachial index (ABI) is used to assess the subclinical form of PAD [22,23].

PanVascular presentation of PAD

Polyvascular presentation among patients with PAD is common. In a previous study enrolled 1802 patients with mean age 80 years, patients with PAD showed the highest rate of polyvascular disease (PVD) in comparison with those with history of stroke and CAD (79% vs. 64% vs. 46%, respectively) [15]. In addition, progression to PVD showed to be more often in patients with PAD (10%) after 3-year follow up than in those with CAD or CVD (almost 4%) [24].

In principle, lesions with large prognostic impact or symptomatic lesions should be treated first. However, patients may be asymptomatic in some of the vascular beds. Consequently, general cardiovascular screening should be considered to detect vascular disease in other territories.

Besides clinical aspects, anatomical factors should be considered to establish optimal treatment sequences for patients with PVD. In addition to treatment of target lesions, endovascular interventions should aim at enabling further vascular interventions. For example, revascularization of iliac arteries should precede intervention of coronary, carotid and visceral arteries. In addition, revascularization of femoral arteries lesions, which require cross-over techniques, should be considered prior to elective endovascular aortic repair.

General clinical approaches to PAD

Clinical classification

As shown in Table 1, the severity of PAD is staged into various clinical stages by both, the Rutherford and Fontaine classifications.

Intermittent claudication

Many patients with intermittent claudication (IC) can be treated conservatively. Mechanical revascularizations are considered when these fail to improve quality of life. Recent reviews show that major amputation is an unlikely outcome of IC, except in patients with diabetes [25–27]. Although, lesions resulting in IC can be located in the aortoiliac and infrapopliteal arteries, the femoropopliteal arteries are most frequently affected (70%) [28]. However,

Table 1 – Fontaine and Rutherford classifications of PAD.

Stage	Fontaine		Rutherford	
	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate/severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		IV	6	Ischemic rest pain

lesions of infrapopliteal arteries are more prevalent in patients with diabetes.

Critical limb ischemia

Critical limb ischemia (CLI) is caused by critically reduced perfusion and represents a severe form of peripheral arterial disease with ischemic pain at rest and/or non-healing skin ulcers or gangrene. The diagnosis of CLI is proven by an ankle systolic pressure less than 50 mmHg or toe pressure below 30 mmHg. However, CLI should also be considered in patients with gangrene or ulcers, with an ankle pressure below 70 mmHg and a toe systolic pressure less than 50 mmHg when they are in the clinical stages Rutherford 4–6 and Fontaine III and IV [5,14]. The significant co-morbid burden of atherosclerotic disease accompanying patients with CLI leads to a tremendously increased risk of cardiac mortality, with estimated 5-year mortality rates exceeding 50% [6,29]. Consequently, the diagnosis of CLI is crucial as it predicts the prognosis of high risk for fatal and non-fatal cardiovascular events and for limb loss. Worth of noting, the 5-year mortality rates in ischemia related diabetic foot ulcers were higher than many common cancers such as prostatic cancer, breast cancer and Hodgkin lymphoma (13–15%) [6,30–32]. Furthermore, the 5-year primary patency rates after aortobifemoral bypass and iliofemoral bypass are worse in CLI in comparison to intermittent claudication (79.8% and 74.1 vs. 89.8% and 86.7, respectively) [33].

Therefore, minimally invasive endovascular techniques with much lower procedural risks offer an important alternative to open surgery in CLI patients with cardiovascular co-morbidities.

Therapeutic approaches to PAD

Clinical stages of PAD range from asymptomatic to gangrene and ulceration, allowing for the application multiple treatment approaches.

Conservative therapy

Conservative therapy includes controlling of cardiovascular risk factor, cessation of smoking and supervised exercise program. Platelet aggregation inhibition is indicated in symptomatic PAD. Further, statins are indicated in asymptomatic and symptomatic patients with PAD as well as optimizing blood pressure.

In the claudication stage (Fontaine II), vasoactive drugs should be considered if walking exercise cannot be performed. Particularly, the use of these drugs could be useful if successful revascularization cannot be achieved. Randomized drug trials showed that cilostazol and naftidrofuryl can significantly improve the walking distance in IC [34,35].

Revascularization

Arterial revascularizations, using either endovascular or surgical techniques are only indicated in symptomatic patients who presented with any one of the following clinical problems: (1) quality of life-limiting IC no longer responsive to conservative therapy; (2) CLI, or (3) acute

limb ischemia (ALI). Many patients with IC can be treated conservatively, with e.g. supervised walking training. Revascularizations are considered when conservative treatment fails to improve quality of life and mobility. In contrast, critical limb ischemia and acute limb ischemia require more urgent interventions to restore blood flow and preserve limbs and lives.

Procedural risk for cardiac events

Cardiac complications may occur depending on patient-related risk factors and on the type of surgery.

Revascularization procedures including open or endovascular procedures according to cardiac risk can be classified into: low-risk, intermediate-risk (peripheral arterial angioplasty, endovascular aortic repair), and high-risk procedures like open aortic surgery, major open vascular surgery, amputation and thromboembolectomy, with estimated 30-day cardiac event rates (cardiac death and myocardial infarction) of <1, 1–5%, and > 5%, respectively [36]. Aortobifemoral bypass and iliofemoral bypass were associated with 4.1%, and 2.7% operative mortality rates, respectively [33].

Procedural factors that influence cardiac risk are blood loss and fluid shifts, the urgency and invasiveness as well as the type and duration of the revascularization procedure. The change in body core temperature, blood loss and fluid shifts has a great influence on the surgical risk.

In patients with cardiovascular co-morbidity, the cardiac risk of surgical procedures must be taken into consideration and guide the choice to less-invasive interventions.

Endovascular management

Advances in endovascular technology and skills over the last decades offer an alternative to open surgery in many patients with cardiovascular co-morbidities with reported equivalent efficacy, lower peri-procedural risk and satisfactory late outcomes [29,37].

Aortoiliac revascularization. A systemic review including 19 cohort studies summarized the patency rates after surgical bypass and endovascular intervention for complex aortoiliac lesions (TASC II C and D). Although, the 4- or 5-year primary patency rate after endovascular interventions was slightly inferior to open surgical bypass, the secondary patency rates showed comparable results (80–98%) of both methods [38].

A meta-analysis which enrolled 16 retrospective studies consisting of 958 patients demonstrated a technical success rate for TASC C and TASC D of 93.7% and 90.1%, respectively. The 12-month primary patency rates were higher in primary stenting than selective stenting (92.1% vs. 82.9%) [39].

Femoropopliteal revascularization

Endovascular versus surgical intervention. A retrospective cohort study comparing primary stenting to femoropopliteal polytetrafluoroethylene (PTFE) bypass in CLI and IC demonstrated patency rate superiority at 12-month and 24-month for endovascular interventions of TASC C lesions compared to bypass surgery (83% ± 6% and 80% ± 7% vs. 81% ± 6% and 75% ± 7%, respectively) [40].

The 4-year primary and secondary patency rates after femoral-popliteal bypass grafts demonstrated no significant difference compared to endovascular PTFE/nitinol self-expanding stent. A prospective randomized study showed primary and secondary patency rates of 59% and 74% after endovascular stenting versus 58% and 71% after surgery [41].

Primary stenting vs. balloon angioplasty. The RESILIENT randomized trial showed improved patency for primary stenting with nitinol stents compared with balloon angioplasty for moderate-length lesions of superficial femoral artery (SFA). The freedom from target lesion revascularization after 1 year (3 years) in the stent group was 87.3% (75.5%) vs. 45.1% (41.8%) for balloon angioplasty [42,43].

Schillinger et al. demonstrated superior patency rates for self-expanding stents to balloon angioplasty alone at 6 and 12 months in long-length SFA lesions. At 2 years rates of restenosis were higher after balloon angioplasty with 69.2% compared with self-expanding stenting with 45.7% [44,45].

FAST trial however, demonstrated no significant difference in restenosis at 12 months for short-length SFA lesions, and, particularly, no benefit in women [46].

Drug eluting balloons vs. uncoated balloons. Drug eluting balloons (DEBs) offer a feasible alternative to stent implantation in infra-inguinal arteries. In multiple randomized clinical trials drug-eluting balloons showed better patency rates compared with uncoated balloon angioplasty [47–49].

A meta-analysis of 4 randomized trials with 381 patients demonstrated superiority of paclitaxel-coated balloons (PCB) over uncoated balloon angioplasty reducing target lesion revascularization (12.2% versus 27.7%) and angiographic restenosis rates of 18.7% vs. 45.5% within 10.3 months median follow-up [50].

Drug-eluting stents. The Zilver PTX trial randomized patients to paclitaxel-coated drug-eluting stents (DES) or balloon angioplasty in femoropopliteal lesions. Primary DES provided higher patency rates at 12-month (83.1%) versus (32.8%) in the PTA group. Furthermore, the recently published 5-year results delivered sustained superiority of primary DES compared with balloon angioplasty (patency rate 66.4% vs. 43.4%). Patency rate was even superior among provisional DES versus provisional bare-metal stent (BMS) (89.9% vs. 73.0%) [51,52].

Sirolimus-coated stents, however, failed to add any advantage at 24 months compared to BMS in the SIROCCO trial [53].

Infrapopliteal revascularization. Infrapopliteal endovascular intervention faces unique challenges such as chronic occlusions, diffuse calcification, complex stenoses and risk of dissection.

Endovascular intervention vs. surgery. In a retrospective analysis enrolling 1023 patients, PTA for infrapopliteal lesions in CLI showed a comparable rate of limb salvage at 5 years in comparison to the bypass group (75.3% vs. 76%) [54].

Drug-eluting balloons. Although, the first 2 randomized trials reported lower rates of restenosis and target lesion revascularization for DEB compared to uncoated balloons at 6- and 12-month for CLI, more recent 1-year

results from the IN.PACT DEEP randomized trial showed higher rates of amputation in the DEB group compared to PTA group (8.8% vs. 3.6%) [42,55,56].

The Paseo-18 Lux DEB, however, showed less rates of major amputation after 12 months compared to standard PTA in BIOLUX P-II trial (3.3% vs. 5.6%) [57]. In principle, there are no sufficient clinical data to support the use of DEB in infrapopliteal lesions.

Stenting including drug-eluting stenting. A clinical trial randomized 161 patients to sirolimus-eluting stents and BMS, treating infrapopliteal focal lesions. Amputation rates were significantly lower in the DES group than in the BMS group (2.6% vs. 12.2%) [58]. Lately, superiority of DES over BMS was demonstrated in 2 randomized trials after 12 months, expressed by higher patency rate and freedom of TLR [59,60]. However, further studies are required to establish the impact of DES on amputation-free survival and limb salvage rates in infrapopliteal lesions.

Endovascular treatment in acute limb ischemia. Acute limb ischemia (ALI) is a sudden (within 14 days) decrease in limb perfusion resulting in a potential threat to the viability of the extremity.

ALI is caused by peripheral embolization of intracardiac thrombus, paradoxical embolism, or in situ thrombosis with preexisting atherosclerosis. ALI is associated with poor prognosis and high amputation rates. The mortality rate is estimated to be as high as 25% with surgical revascularization [61].

Catheter-directed thrombolysis. Although, systemically administered thrombolysis has no role in the treatment of patients with ALI, the effective role of catheter-directed thrombolysis (CDT) has been confirmed.

In a randomized trial comparing CDT with open surgery, the patient survival rate at 12 months was significantly higher for CDT in comparison to open surgery (84% vs. 58%) [61,62]. The TOPAS trial demonstrated an equivalent rate of amputation-free survival at 12 months for CDT and surgery (65% vs. 66.9%) [62]. The 6-month limb salvage, however, was significantly higher for the CDT than for surgery in the STILE randomized trial (89% vs. 70%) [63].

Rotational thrombectomy for acute limb ischemia. Rotational thrombectomy are considered to excise plaque and reduce the thrombus burden which may reduce the application of thrombolysis.

A retrospective analysis showed a 94.7% technical success rate and 49% to 51% rate of restenosis at 12-month follow-up [64].

Conclusion

The high prevalence of polyvascular presentation in patients with PAD requires a multidisciplinary approach individually tailored to each patient to optimize short- and long-term prognosis. The cardiovascular burden in patients with PAD highlights the need of minimally invasive therapeutic techniques.

Conflict of interest

None declared.

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None.

Ethical statement

Authors state that the research was conducted according to ethical standards.

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