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Přehledový článek | Review article

Panvascular disease – Epidemiology and prevention

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SOUHRN

Ateroskleróza je progredující generalizované onemocnění postihující všechna tepenná řečiště.
K rozvoji aterosklerózy dochází již v mládí [1] a časem se stav pacienta pomaleji nebo rychleji zhoršuje v závislosti na přidružených rizikových faktorech a genetickém pozadí.
Vícečetné postižení cév neboli panvaskulární postižení (panvascular disease, PVD) je definováno jako současná přítomnost klinicky významných aterosklerotických lézí v nejméně dvou hlavních cévních řečištích. Jedná se tedy o situace, kdy jsou v pacientově anamnéze zaznamenány symptomy ischemie (ať již v současnosti, v přítomnosti jiných onemocnění, nebo v různých časových obdobích) spolu s přítomností četných subklinických tepenných lézí s významným rizikem budoucích klinických projevů postihujících dvě řečiště nebo více různých řečišť.
I když se studiu prevalence PVD v obecné populaci dosud nevěnovala dostatečná pozornost, její hodnota se prudce zvyšuje s věkem, kdy dochází k hromadění častých faktorů kardiovaskulárního rizika. U pacientů s PVD existuje zvýšené riziko dalších kardiovaskulárních příhod, ať již fatálních, nebo nefatálních. Naopak se lze často setkat s nedostatky v komplexní léčbě těchto pacientů. Řada studií shodně zdůrazňuje nedostatečnou léčbu těchto pacientů ve srovnání s jedinci s postižením pouze jedné tepny, zvláště pokud nebyla prokázána přítomnost významné přidružené ischemické choroby srdeční.
Je proto třeba vypracovat postup komplexního vyšetření kardiovaskulárního systému v rámci screeningu/prevence u asymptomatických pacientů s cílem primárně stanovit jejich kardiovaskulární riziko.

Keywords:
Epidemiology
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ABSTRACT

Atherosclerosis is a progressive, general disease, affecting all arterial beds. Atherosclerosis starts in the youth [1] and aggravates in time, more or less quickly, according to the associated risk factors and genetic background.
The simultaneous presence of clinically relevant atherosclerotic lesions in at least two major vascular territories defines the multisite artery disease or panvascular disease (PVD).
This represents the situations where ischemic symptoms are present, concomitant, or successive during patient's history and/or in the presence of multiple subclinical arterial lesions at significant risk of clinical manifestation in the future, affecting two or more distinct territories.
The prevalence of PVD in general population is poorly studied but is sharply increasing with age and accumulation of common cardiovascular risk factors. Patients with PVD are at increased risk of further cardiovascular events, either fatal or nonfatal. In contrast, gaps in comprehensive care of these patients are frequent. Many studies are concordant to underline poorer management of these patients compared to single-bed artery disease, especially if there is no evidence of significant associated coronary artery disease.
Therefore, a full cardiovascular work-up should be proposed in a screening/preventive program in asymptomatic patients in order to primarily assess their cardiovascular risk.

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Introduction

Atherosclerosis, a general disease, shares common major risk factors for different arterial localizations [1].

Multiple artery lesions are common in patients with clinical atherosclerotic involvement in one vascular bed.

Panvascular artery disease (PVD) is defined by the simultaneous presence of clinically relevant atherosclerotic lesions in at least two major vascular territories [2]. Although patients with PVD are regularly encountered in clinical practice, robust data on the epidemiology and management of these patients are scarce.

Epidemiology

While the epidemiology of any clinical presentation of the atherosclerotic disease is widely studied, the prevalence of panvascular disease (PVD) in general population is poorly assessed. Studies are mostly focused on the coexistence of coronary artery disease (CAD), lower-extremity artery disease (LEAD), cerebrovascular disease (CBVD) and renal artery disease (RAD) in patients presenting any of these conditions.

The proportion of subjects with at least 2 localizations increases with age, from 0.04% between 40 and 50 years of age to 3.6% in the 81–90 years age group and 6.6 % in the 91–100 years age group [3]. The increased prevalence and probability of the PVD with age is presented in Fig. 1.

Among patients with established cardiovascular disease, the prevalence of PVD is at least 20% [4–8]. The epidemiology of PVD is summarized in Table 1

In a systematic review of 7512 coronary artery bypass graft surgery (CABG) patients who had carotid duplex screening, a prevalence up to 15% of 50–99% of carotid stenosis was reported [9].

The most recent study, reporting outcome in 3233 patients undergoing open heart surgery, described unilateral carotid stenosis 50–99% in 11.1%, bilateral 50–99% stenosis in 5.6%, and unilateral occlusion in 1.3% among the 306 patients undergoing isolated CABG who were scanned preoperatively [10]. The most common factors for predicting carotid stenosis in CABG patients include: increasing age, history of CBVD, presence of a carotid bruit, multivessels CAD, and clinical or subclinical LEAD [11,12].

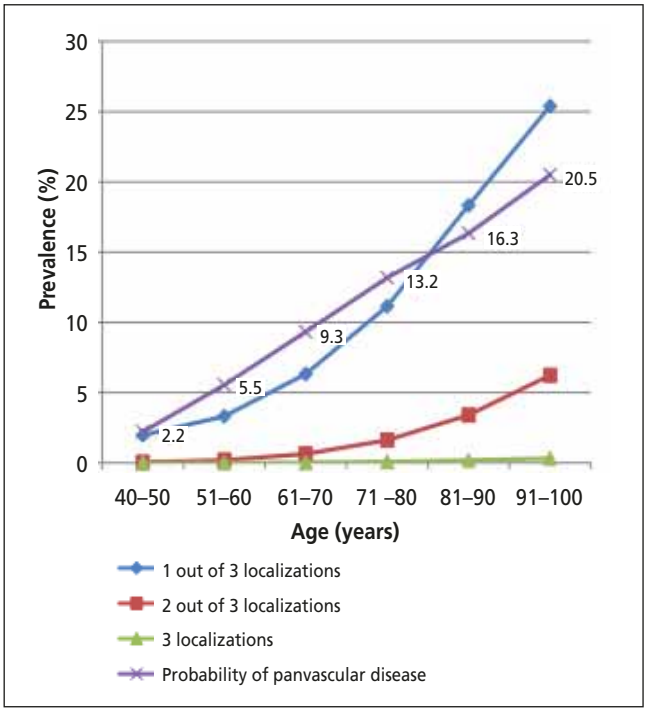

Fig. 1 – Prevalence and probability of panvascular disease according to age. Adapted from Savji et al. [3].

Overall, the prevalence of significant carotid stenosis in stable CAD patients is relatively low, but increases concurrently with the severity of CAD [13]. In a general review of 20,395 consecutive CAD patients, the prevalence of carotid stenosis >70% was 5% [13]. Among patients undergoing coronary angiography, the prevalence was as high as 7.0% in case of 3-vessel disease and 10.1% in case of left main trunk disease [14].

Carotid stenosis is also frequently associated with LEAD. In a population-based study including 3.67 million self-referred subjects with a mean age of 64 years, subjects with an ankle-brachial index (ABI) < 0.90 had a higher prevalence of carotid stenosis (>50%) than those without (18.8% vs. 3.3%; $p < 0.0001$) [15]. In multivariate analysis, both symptomatic (OR 3.7) and asymptomatic LEAD (OR 2.9) were associated with increased risk for carotid disease. Increasing severity of LEAD was also associated with greater odds of carotid disease, up to a 7.6 OR for patients with

Table 1 – Prevalence of associated atherosclerotic disease in additional vascular territories.

Leading disease	Associated disease			
	CAD	CAS > 70%	LEAD (ABI < 0.90)	RAS ≥ 75%
CAD	NA	5–9% [9–11]	7–16% [6,11,12]	5–15% [5,11,13,14]
Single-vessel CAD	NA	3–5 % [15]	7% [11]	4% [11]
3-vessel CAD	NA	10–12% [15]	27% [11]	18% [11]
CAS > 70%	39–61% [11,16,17]	NA	20% [11]	
LEAD (ABI < 0.90)	25–70% [4,11,18]	14–19% [19,20]	NA	10–23% [11]

Adapted from ESC 2017 Guidelines on PAD [2].
ABI – ankle brachial index; CAD – coronary artery disease; CAS – carotid artery stenosis; LEAD – lower extremities artery disease; RAS – renal artery stenosis.

ABI ≤ 0.40. In a meta-analysis of 19 studies including a total of 4573 patients, the prevalence of carotid stenosis >70% in patients with LEAD was reported at 14% [16]. Risk factors for the association of carotid disease and LEAD include age, smoking, and concomitant CAD; interestingly, associated carotid disease appears twice as common among LEAD patients than among CAD patients [17].

LEAD often coexists with CAD, but is rarely diagnosed as patients are mostly asymptomatic, or may not reach the pain threshold because of limiting angina and/or dyspnoea. In primary care studies, the ABI allows detection of LEAD in almost one fourth of patients with history of CAD, with highest prevalence in diabetic individuals [18,19]. In patients hospitalized for CAD, the prevalence of ABI < 0.90 ranges between 7% and 28% [6,17,20,21], while clinical examination allows detection of LEAD in up to 14% [21,22]. Importantly, patients with isolated LEAD appear to progress more rapidly to PVD compared with patients with isolated CAD or CBVD (10% vs. 4% after 3 years of follow-up in the REACH registry) [23].

In 2 recent studies including 2445 consecutive patients with angiographically-proved CAD, the measurement of ABI revealed LEAD in 13–16% of the cases [24,25]. The presence of left main stenosis and multivessel CAD were independent predictors of concomitant LEAD.

Conversely, at least one-third of patients with LEAD have a history and/or ECG signs of ischemic heart disease, while two-thirds have an abnormal stress test, and up to 70% present at least single vessel disease at coronary angiography [26]. The prevalence of CAD is 2- to 4-fold higher in patients with LEAD versus those without LEAD. In the CONFIRM (*COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter*) registry, in 7590 patients with LEAD without history and symptoms of heart disease, the prevalence of obstructive CAD at coronary CT was 25% [27]. In the REACH registry, 57% of the participants with LEAD also suffered from CAD [4].

Patients with LEAD showed more extensive and calcified coronary atherosclerosis, constrictive arterial remodelling, and greater disease progression [28]. In the PEGASUS-TIMI 54 trial, 5% of the 21,162 patients with prior myocardial infarction (1–3 years before randomization) had known LEAD [29].

Importantly, in patients with severe CAD, the presence of symptomatic or asymptomatic LEAD is associated with high rates (almost 20%) of carotid stenosis [11]. Most epidemiologic studies report the frequency of CAD in patients suffering a stroke; however, considering the complex aetiology of stroke, these data do not represent the prevalence of CAD in patients with severe carotid stenosis. In a recent study, the prevalence of coronary stenosis >50% at CT scan among 276 patients with non-cardioembolic ischemic stroke or transient ischemic attack was 18%, being 4-fold higher in patients with carotid stenosis >50% [30]. In a prospective investigation in 390 patients undergoing elective carotid artery stenting, systematic coronary angiography showed the presence coronary stenosis ≥70% in 61% of patients [31].

CAD might also be associated with renal artery disease (RAD). In recent studies on patients with CAD undergoing coronary angiography the prevalence of RAD (stenosis ≥75%) was reported between 5% and 15% [17,32,33], and is twice more common in females than in males [32]. Hypertension, diabetes, multivessel CAD, chronic kidney disease stage ≥3, and concomitant LEAD are more prevalent in patients with significant RAD [32,34].

The prevalence of RAD (stenosis >60%) is also reported between 10% and 23% in studies on concomitant assessment of renal arteries during angiography for LEAD, and can reach 40% in patients with aorto-iliac disease requiring revascularization [17]. Risk factors for the association of RAD and LEAD include age, female sex, aorto-iliac LEAD, critical limb ischemia, smoking, hypertension, and renal failure [17].

In patients with PVD, mesenteric artery disease may also be relatively common. In patients undergoing routine cardiac catheterization the prevalence of visceral artery stenosis was 14%, situated in almost 11% for coeliac axis and 3% for superior mesenteric artery [35] while in patients with LEAD and RAD, 27% had ≥50% stenosis in the mesenteric arteries [36].

In patients with atherosclerotic disease in one vascular site, the presence of co-existing disease in a different vascular bed is associated with a higher risk of recurrent symptoms and complications in the first site. In the REACH registry, the incidence of CV death, MI, stroke, or hospitalization for atherothrombotic events at 1 year increased with the number of symptomatic sites, ranging from 5% for patients with risk factors only to 13%, 21%, and 26% for patients with one, two, and three symptomatic sites, respectively ($p < 0.001$ for trend) [37]. At 3 years, the corresponding rates of events were 25% for patients with symptomatic vascular disease in one vascular site and 40% for patients symptomatic in multiple vascular sites ($p < 0.001$) [23]. Patients with CAD + LEAD + CBVD had a 1.5-fold increase in-hospital and 3-year mortality [5]. These data were confirmed in a large Australian multi-centre PCI registry, where PVD was an independent predictor of long-term mortality (adjusted HR 1.7) [38] and underline the necessity of preventive strategies in order to limit the progression of the atherosclerotic disease.

Prevention

Although there is no specific study demonstrating that screening for PVD has an impact on prognosis, the dismal outcome of patients with PVD supports a general recommendation to screen (non-invasively) for PVD for prognostic stratification of patients with known atherosclerotic disease and the prevention of atherosclerosis [3].

The preventive approach to patients with PVD includes two aspects. The first is to detect the arterial disease in others localisations and assess the related specific cardiovascular (CV) risk. The second aspect, of the outmost importance in the management of these patients, is related to the general CV prevention as single bed or panvascular disease share the same CV risk factors (Fig. 2).

Prevention includes CV risk factor management, including pharmacological therapy as well as non-pharmacological measures such as smoking cessation, healthy diet, weight loss and regular physical exercise [39,40].

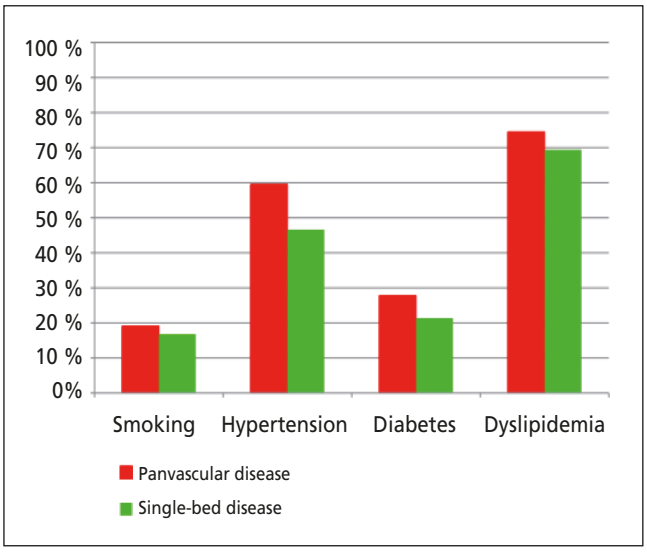

Fig. 2 – Panvascular and single-bed disease associated cardiovascular risk factors. Adapted from ESC guidelines [40].

A robust body of evidence supports the benefits of smoking cessation in reducing CV events, overall mortality, especially in patients with cerebrovascular disease and LEAD [41]. The management and support to promote smoking cessation has extensively been addressed in 2016 ESC guidelines on CV disease prevention. In managing tobacco users' patients, the 5 A's road map is recommended:

(1) **A**ssess behaviours and dependence by the Fagerstrom's questionnaire or biomarkers such as exhaled carbon monoxide concentrations.
(2) **A**dvise about health risks and benefits of change.
(3) **A**gree on a collaborative set of goals.
(4) **A**ssist with support and pharmacotherapy: nicotine replacement therapy and/or bupropion or varenicline.
(5) **A**rrange follow ups.

In view of the strong relationship between active or passive smoking and CV diseases, removal of this modifiable risk factor is of particular importance [42].

Antihypertensive, lipid-lowering, and antithrombotic pharmacological treatments complete the initial management of PAD patients.

In diabetic patients, optimal glucose level control should be obtained with a target $HbA_{1c} < 7\%$ [43].

In observational and limited randomized clinical trials statins showed reduction in all-cause mortality and CV events in PAD subjects (ABI < 0.9 to critical limb ischemia) [44,45]. In the REduction of Atherothrombosis for Continued Health (REACH) registry, statin use was associated with an approximately 17% lower rate adverse cardiovascular events (the composite of cardiovascular death/myocardial infarction/stroke) [46].

All patients with PADs should have their serum low-density lipoprotein cholesterol (LDL-C) reduced to <70 mg/dL or decreased by >50% if the initial LDL-C level is between 70 and 135 mg/dL [47].

Lowering systolic blood pressure (SBP) reduces the risk of stroke and cardiovascular events. According to the current ESC/European Society of Hypertension guidelines [48], a target BP of <140/90 mmHg was recommended, except in patients with diabetes for whom diastolic BP ≤ 85 mmHg was considered safe. Recently the SPRINT Trial compared standard (SBP target <140 mmHg) and intensive (<120 mmHg) treatment in 9361 hypertensive ≥50 years adults with an average CV risk of about 2%/year (Framingham 10-year risk score of 20%) [49]. All-cause mortality and the primary composite outcome of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure and CV disease were reduced by about 25% in the intensive group. Should these results be also extended to patients with PVD is not yet defined. In fragile elderly patients, BP goals should be adapted.

In patients with PVD appropriate lifestyle and salt intake (between 5 and 6 g of salt/day) are recommended. Diuretics, beta-blockers, calcium antagonists, ACE-inhibitors, and angiotensin receptor blockers are all suitable for antihypertensive treatment initiation and maintenance, either as monotherapy or in combinations. However, some classes can be preferred according to comorbidities, and different combinations are possible. Interestingly HOPE (ramipril) and ONTARGET (ramipril/telmisartan) trials have shown that angiotensin converting enzyme inhibitors and angiotensin receptor blockers significantly reduce cardiovascular events in vascular patients [50,51].

The use of oral antiplatelet agents is part of secondary prevention measures to prevent PVD-related events. A number of antiplatelet strategies are available. The recent COMPASS study (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease) might also support the benefit of the direct oral antithrombotic drugs for the prevention of PVD [52].

Though different localizations of PVD share common risk factors of atherosclerosis, the impact of each factor, and/or data available, differ according to the disease site. However, for the overall prognosis it is important to realize that the atherosclerosis is often generalized and that that subjects are at increased risk of cardiovascular disease.

For the management of PVD patients, clinical status and comorbidities should be considered, in addition to the lesion sites. Generally, the treatment strategy should be decided on a case-by-case basis within a multidisciplinary team and focus first on the symptomatic vascular site.

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None declared.

Funding body
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Ethical statement
Authors state that the research was conducted according to ethical standards.

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