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The link between impaired oxygen supply and cognitive decline in peripheral artery disease

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ABSTRACT

Although peripheral artery disease (PAD) primarily affects large arteries outside the brain, PAD is also associated with elevated cerebral vulnerabilities, including greater risks for brain injury (such as stroke), cognitive decline and dementia.

In the present review, we aim to evaluate recent literature and extract information on potential mechanisms linking PAD and consequences on the brain. Furthermore, we suggest novel therapeutic avenues to mitigate cognitive decline and reduce risk of brain injury in patients with PAD.

Various interventions, notably exercise, directly or indirectly improve systemic blood flow and oxygen supply and are effective strategies in patients with PAD or cognitive decline. Moreover, triggering protective cellular and systemic mechanisms by modulating inspired oxygen concentrations are emerging as potential novel treatment strategies.

While several genetic and pharmacological approaches to modulate adaptations to hypoxia showed promising results in preclinical models of PAD, no clear benefits have yet been clinically demonstrated. We argue that genetic/pharmacological regulation of the involved adaptive systems remains challenging but that therapeutic variation of inspired oxygen levels (e.g., hypoxia conditioning) are promising future interventions to mitigate associated cognitive decline in patients with PAD.

Introduction

Manifestation

Peripheral artery disease (PAD) is a systemic and progressive vascular disorder affecting medium to large arteries (except coronary or cerebral arteries) characterized by either stenosis, occlusion or both,[1] leading to impaired blood delivery (i.e., ischemia) and thus oxygen supply (i.e., hypoxia) to peripheral tissues. PAD is primarily caused by atherosclerosis and has a complex genetic component.[2] It may affect the four limbs and visceral arteries but most often affects the lower extremities. The clinical presentation of lower extremity PAD may vary from asymptomatic (>50% of patients with PAD) to severe limb ischemia (about 1%) with a prevalence of amputation of 3–4% among all patients with PAD. The typical presentation is intermittent claudication, which refers to recurring pain, feelings of exhaustion, numbness, weakness, or cramps during exertion. These symptoms occur in around 10% of patients with PAD and up to 20–40% may present with atypical leg symptoms.[3–5] Although cerebral arteries are not primarily affected in PAD, detrimental effects on brain and cognition are increasingly recognized and likely associated with reduced oxygen availability. The aim of the present review is to summarize the evidence of association

Abbreviations: ABI, Ankle-brachial index; CASI, Cognitive Abilities Screening Instrument; CHD, Coronary heart disease; CI, Confidence interval; CVD, cardiovascular disease; HIF, Hypoxia-inducible factors; HR, hazard ratio; HRQOL, Health-related quality of life; IC, intermittent claudication; IQ, interquartile; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; Nrf2, nuclear factor-E2-related factor; PA, Physical activity; PAD, Peripheral artery disease; PBMCs, Peripheral blood mononuclear cells; QoL, Quality of life; VEGF, vascular endothelial growth factor; VO_{2max}, Maximal aerobic capacity; UPR, Unfolded protein response.

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between PAD and impaired oxygen supply to the brain and to evaluate the implications for potential prevention of cognitive impairment. We will focus on the role of exercise and how the controlled variation of oxygen supply could be employed to ameliorate cognitive function in patients with PAD.

Epidemiology

Due to the large proportion of asymptomatic cases, the real prevalence of PAD is unknown, but it has affected growing numbers of people in the last decades, reaching an estimated 202 million cases globally in 2010 [6] and 236 million in 2015.[7] For a detailed epidemiologic assessment of PAD, the reader is referred to the recent review of Aday and Matsushita.[8] The risk to develop PAD increases steeply with advancing age,[6] affecting about 30% of men and 40% of women above the age of 80.[9] All modifiable risk factors for atherosclerotic cardiovascular diseases (CVD), such as diabetes, hypertension, smoking and dyslipidemia, increase the risk to develop PAD.[10] Cigarette smoking both increases the risk to develop PAD and intermittent claudication[11] and is one of the most important risk factors for PAD progression.[5] A sedentary lifestyle is a further independent risk factor to develop PAD,[12] while exercise is a protective factor and important treatment strategy, as discussed below.

Although PAD is the third most common cause of mortality from CVD after coronary heart disease (CHD) and stroke[6] and is a major reason for limb amputations, it remains poorly understood, under-diagnosed and under-treated.[3–5] Despite the frequent absence of intermittent claudication or other major symptoms, patients with PAD experience reduced functional capacities, impaired quality of life (QoL)[13,14] and increased risks to develop other CVD morbidities.[3]

Diagnosis

Prompt diagnosis of PAD is crucial to avoid the detrimental consequences of the disease and is impeded by the frequent asymptomatic nature of early stages. Asymptomatic PAD, however, is associated with similar morbidity and mortality risks like PAD with claudication.[15] A considerable proportion of asymptomatic patients develop intermittent claudication symptoms and experience acute or critical limb ischemia, the ultimate stage of PAD. This in turn can lead to amputation and death and requires urgent surgical or endoluminal revascularization.[5] The simple measurement of the ankle-brachial index (ABI) is a cost-effective, noninvasive diagnostic tool for PAD based on the ratio of the systolic blood pressure measured at the ankle to the one measured at the brachial artery and has an estimated 95% sensitivity and 99% specificity for PAD.[4] An ABI smaller than 0.9 indicates PAD (arterial stenosis due to atherosclerosis $\geq$50%), while people without PAD have an ABI of 1.10 to 1.30. PAD is classified as mild when the ABI is between 0.9 and 1.09.[16] Duplex ultrasound scanning (to determine arterial structures and blood flow), transcutaneous oxygen pressure measurements (assessing local tissue oxygenation) and pulse volume recordings (assessing local tissue perfusion) are additional simple, non-invasive diagnostic techniques. Due to their reliance on technical expertise and error-prone interpretation, especially in some patient populations, they each have specific limitations for PAD diagnosis.[5] Second line imaging approaches are the radio-contrast agent-reliant computed tomographic angiography, the more expensive – but non-invasive – magnetic resonance angiography and digital subtraction angiography.[5] The latter, however, is expensive and invasive and thus is reserved for cases with intention to perform lower extremity revascularization (endovascular treatment or open surgery).[5]

Per definition cerebral arteries are not primarily affected in PAD, but cerebral vascular damage is frequent in patients with PAD. Consequently, several secondary effects on the brain, such as cognitive impairments, are increasingly recognized.[17–21] This association is discussed in the next section.

Vascular deficits, reduced oxygen supply and cerebral dysfunction

The emerging concept of "polyvascular disease" refers to a condition characterized by clinically important atherosclerotic changes in different arterial beds that might lead to detrimental cerebrovascular (cerebrovascular disease), cardiac (coronary artery disease) or peripheral vasculature (PAD) outcomes.[8] In polyvascular disease, vulnerabilities may exist also in vessels that are not related to the primarily affected arterial bed, explaining related comorbidities of vascular diseases. Accordingly, the obstruction of arteries in PAD can cause reduced blood flow and thus impaired oxygen and nutrient supply even in distant tissues (see Fig. 1). This is a central driver of the pathology of PAD and various other diseases, such as diabetic retinopathy or CHD.[22] PAD therefore is also a risk factor for other CVD complications and patients with PAD (with and without CHD or cerebral artery disease) have increased mortality risks from CVD or cerebrovascular events.[4] PAD further frequently indicates obstructive atherosclerotic disease of cerebral vessels[5] and accordingly is associated with a 35%-increased risk for stroke.[23] Vascular pathologies, including PAD, are frequently associated with reduced cognitive performance and the development of dementia, independent of well-established cognitive effects of age and education.[24] Similarly, indicators of atherosclerosis have been linked to the development of dementia.[25] CVDs represent a general risk factor for dementia but among them PAD seems to increase the vulnerability for dementia most.[26]

Cognitive dysfunction – that often seems to be largely independent from comorbidities and other CVD risk factors – emerges as a common feature in people affected by PAD as reviewed previously.[19,27] A recent review[18] summarizes reported detrimental effects of PAD on cognitive functions, which include nonverbal reasoning, verbal fluency and decreased information processing speed. In addition, PAD is associated with an increased risk to develop dementia. A prospective community based study on 3734 men (71–93 years) demonstrated the association of a low ABI with increased dementia risk (hazard ratio (HR) 1.66, 95% confidence interval (CI) 1.16–2.37) that was particularly strong for vascular dementia (HR 2.25, CI 1.07–4.73) and for Alzheimer's disease in carriers of the disease-associated allele apolipoprotein E epsilon 4 (HR 1.43, CI 1.02–1.96).[28] Together these findings support the notion of dementias, including Alzheimer's disease, as vascular disorders[29,30] and a link with PAD. Large longitudinal studies to confirm the correlation between ABI and the progression of cognitive decline are still needed.

On the molecular level, various processes overlap in PAD and neurodegenerative diseases, such as dementias. This suggests potential inter-relations in their pathogeneses. Many of the molecular overlaps are associated with oxygen supply or consumption, the focus of the subsequent section.

Vascular deficits in PAD and cognitive dysfunction

Interdependent pathological hallmarks of neurodegenerative diseases include oxidative stress, inflammatory processes and mitochondrial dysfunction, which often result in vascular deficits.[18] Conversely, also impaired peripheral vasculature function (as is characteristic for PAD) can compromise brain function. This has for example been shown in rats, in which experimental ischemia-reperfusion of the lower limbs caused substantial brain deficits: Lower limb ischemia for 2 h and subsequent reperfusion caused synaptic excitement, loss of pyramidal cells and synaptic plasticity deficits in the hippocampus.[31] Another group reported cognitive dysfunction (as assessed by the Morris water maze test) and oxidative stress, reduced antioxidant superoxide dismutase levels as well as morphologically discernible neuronal injury, also in the hippocampus of rats following 3 h limb ischemia and subsequent reperfusion.[32]

Impaired responses to hypoxia and associated compromised oxygen supply have emerged as important factors in the development and/or

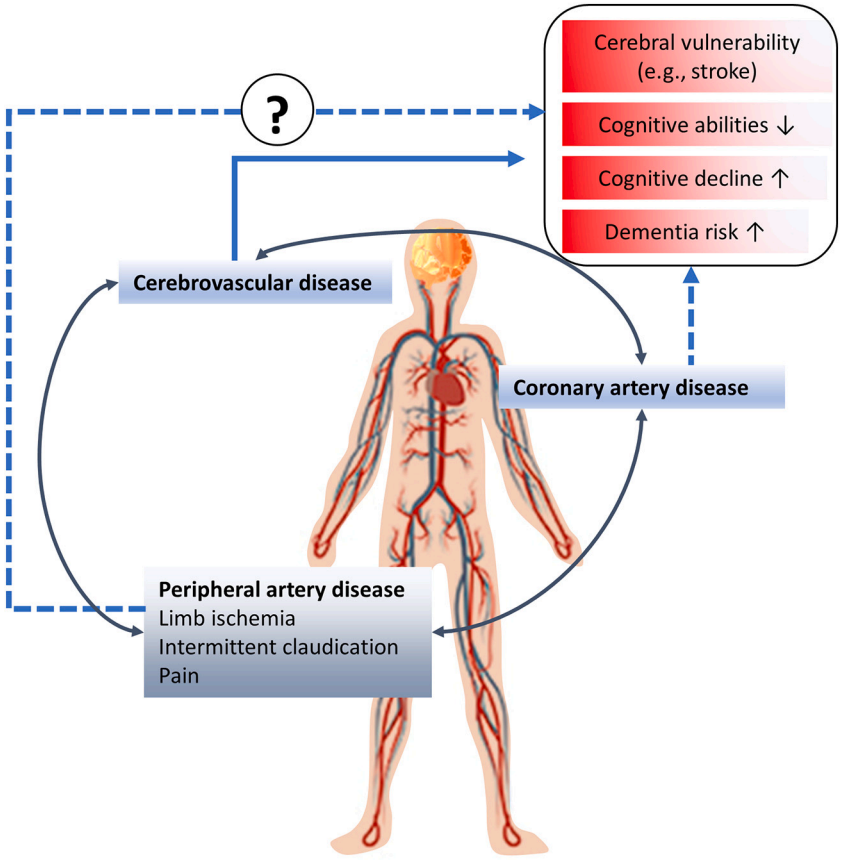

Fig. 1. *Vascular diseases and brain vulnerability.* Cerebrovascular disease has detrimental consequences on brain function.

disease progression of many genetic and age-related neurological diseases, including Huntington's disease,[33] Parkinson's disease[34–37] and dementias.[38–40] While young and healthy brain is able to adapt to moderate oxygen supply deficits, this may not be the case in the aging brain or in certain pathological conditions.[38] For example, a long-term adaptation to hypoxia is angiogenesis leading to increased blood supply to tissues. In Alzheimer's disease model mice and in the brain of Alzheimer's disease patients, it has been shown that angiogenesis is impaired in proximity to amyloid-beta plaques, leading to non-productive angiogenesis (i.e. increased angiogenic sprouting and branching that does not improve perfusion) and blood vessel pathologies.[41]

Major adaptations to cope with reduction in oxygen supply are regulated by hypoxia-inducible factors (HIFs), crucial coordinators of hypoxia responses. Alpha-subunits of HIFs are continuously degraded in normoxia via prolyl hydroxylases but stabilize under hypoxia. They then dimerize with beta-subunits and trigger a complex transcriptional program aiming at lowering oxygen dependency (e.g., by upregulation of glycolysis and downregulation of oxidative phosphorylation) and improving oxygen supply by promoting erythropoiesis, vasodilation and angiogenesis.[42] HIFs are importantly involved in all aspects of neovascularization, including formation, maturation, patterning and function of vessels.[22] The abnormal activation of the HIF-1 pathway has for example been demonstrated in models of Alzheimer's disease and in the hippocampus of Alzheimer's disease patients.[39]

HIFs are also involved in the pathogenesis of atherosclerotic disease, including PAD ([43] and see chapter 5), as well as in neurodegenerative diseases, leading to dementia.[44–46]

Furthermore, a genome-wide association study recently revealed several genetic risk factors unique to PAD, indicating genetic links of PAD with diseases of other vascular beds, including cerebral vessels, suggesting pathways related to lipids, hypertension and diabetes to be affected.[47] These findings support a partially overlapping genetic basis of PAD and cerebrovascular pathologies.

Mitochondrial oxygen consumption in PAD

The main consumers of oxygen at the cellular levels are mitochondria, which produce cellular energy, signal cellular damage and injury and are essential for fundamental metabolic processes. Perfusion deficits arising from PAD impact on mitochondrial function. These mitochondrial dysfunctions induced by PAD are increasingly discussed.[3,48,49] Metabolic impairment in patients with PAD includes increased plasma levels of acylcarnitines - required to transport long-chain fatty acids into mitochondria for beta-oxidation-, likely due to deficits in mitochondrial oxidative metabolism.[50] Both revascularization processes and physical exercise benefit mitochondrial function. The beneficial effects of these interventions on PAD may thus depend at least partially on mitochondrial improvements.[48,51,52] Importantly, brain mitochondria benefit from physical exercise by signaling from skeletal muscle mitochondria.[53] It is possible that mitochondrial dysfunction associated with PAD interferes with such signaling and reduces protective signals from peripheral mitochondria to the brain, contributing to mitochondrial dysfunction in the brain, a core pathological feature of neurodegenerative diseases.[54]

In summary, PAD and neurodegenerative diseases are characterized by overlapping and probably interdependent deficits of different molecular components, especially related to oxygen supply. This leads to compromised responses to hypoxia, vascular deficits and mitochondrial dysfunctions.

PAD and cerebral and cognitive damage

A recent meta-analysis showed that severe atherosclerosis is a

significant risk factor for both cognitive decline and dementia, also independent of stroke.[55] These authors pointed out specifically the insufficient availability of data on the influence of PAD (in absence of stroke) on cognition. However, the study of Newman and colleagues showed that PAD (patients with stroke excluded) increased the likelihood to develop dementia 2.4-fold (95% confidence intervals = 1.4–4.2).[26]

Gardner and colleagues[56] recently observed that PAD was associated with cognitive deficits; particularly for verbal memory, attention and working memory. These authors interpreted these results as a support for aggravated aging-related vascular deterioration due to symptomatic PAD that also affects the brain and its blood supply.

To assess the available evidence for vascular vulnerabilities of the brain and functional consequences on cognition for PAD, we performed a literature search on pubmed using the search terms "peripheral artery disease" and ("brain" OR "cerebral" OR "cognitive"). The titles and abstracts of the resulting 403 hits (up to 30th May 2022) were screened for work investigating or reviewing cognition and/or brain insults related to disturbed blood supply in PAD. In addition, relevant references of the screened articles were considered. Due to previous systematic evaluation of cognitive impairment and PAD[27] and a pronounced increase in the interest in this topic (based on increased publication numbers) from around 2010, only articles published in 2010 or after (335 results) were considered for inclusion in Tables 1 and 2.

Studies reporting either an impact of PAD on cognitive or psychological brain functions or the interplay of cerebral damage (e.g., stroke) and PAD were selected. Studies evaluating pharmacological interventions on cardiovascular outcomes in populations of PAD patients only were not considered.

Reports on the risk of cerebrovascular insults in PAD since 2010 are summarized in Table 1.

Patients with systemic vascular disease (including PAD) have been reported previously to be at higher risk for cerebrovascular injuries, such as silent brain infarction[82] and ischemic stroke [23,83].

The findings in Table 1 overall support an increased vulnerability of both preclinical and symptomatic patients with PAD to cerebrovascular injuries, such as ischemic stroke, and mortality from such events.[57,61,62,65,67–69] Some reports suggest a differential vulnerability according to specific pathologies in subtypes of PAD.[58,59] An advanced stage of PAD[70] or the combination with comorbidities like diabetes appear to further increase the cerebral vulnerability of patients with PAD.[64]

On the other hand, the risk for intracerebral hemorrhage was not different in stroke patients with or without PAD[60] and intracranial artery stenosis could not be predicted based on presence of PAD in patients undergoing coronary bypass surgery.[66] PAD also did not increase the risk for recurrent stroke after a first incidence of acute ischemic stroke.[68] Importantly, these populations of stroke and coronary bypass surgery patients also consist of many individuals with high other CVD risk factors and therefore the latter results do not indicate that PAD represents no risk factor for cerebrovascular injury.

Taken together, PAD is a risk factor for cerebrovascular injuries, although this depends on a variety of factors, in particular the type and disease stage of PAD and the presence of comorbidities. After experiencing a severe cardiovascular event, patients with PAD may not be more vulnerable to subsequent cerebrovascular damage, as compared to patients that suffered a similar injury.

The cerebrovascular vulnerability of patients with PAD raises the question, whether PAD is also associated with impaired brain function, even in the absence of severe events. Guerchet and colleagues[27] performed a systematic review in 2011 and reported significant associations between a low ABI (<0.90) and cognitive impairment and dementia in general or Alzheimer's disease (the most common form of dementia). They conclude that the ABI informs about the risk to develop cognitive disorders. Recent research on this topic is summarized in Table 2.

Table 1
PAD and vulnerability to cerebrovascular insults.

Subjects	Study design	Main results	Ref
A total of 39,834 people were characterized by ABI: 17,091 with low ABI (age 69.1 ± 12.7, 57% males), 17,672 with normal ABI (age 62.2 ± 15.1, 54% males), 5071 with elevated ABI (age 71.0 ± 12.4, 71% males)	ABI data of all adult patients on whom lower extremity physiology studies had been performed from 1996 to 2018 in the Mayo Clinic health system were retrospectively extracted. The median follow-up duration was 4.59 years	PAD was associated with higher ischemic stroke risk compared to normal ABI; for moderate PAD: HR 1.22 (95% CI 1.10–1.35) and for severe PAD: HR 1.19 (95% CI 1.02–1.40). Abnormal ABI was associated with higher mortality risk from all causes in a severity-dependent manner, e.g., severe PAD: HR 3.07 [95% CI 2.88–3.27]	57
226 symptomatic PAD patients	Registered participants of the prospective PureASO registry were followed up after lower limb revascularization	5 years after revascularization 31% of patients had no cerebrovascular disease. Crural arteries – compared to other lower limb artery segments - burden was associated with higher risk of mortality (adjusted HR 2.07, CI 95% 1.12–3.28, $p = 0.021$) and cerebrovascular events	58
289 acute ischemic stroke patients; 37.4% of them with PAD (age 72.2 ± 9.7, 60.2% male) the others without PAD: 65.7 ± 11.6, 60.8% male	Lower-extremity ultrasonography was used to determine the atherosclerosis location	Subclinical PAD (in 37.4% of patients) was associated with poorer functional outcome after stroke, the location of cerebral atherosclerosis differed according to the location of PAD (above-popliteal artery or below-tibialis artery)	59
Of 2555 stroke patients (age 73.9 ± 13, 49.4% males), 640 had co-existing CVD (age 78 ± 10, 55.3% males), of which 103 had peripheral only or peripheral and coronary CVD	Consecutive patients with transient ischemic attacks or ischemic stroke of the Oxford Vascular Study were studied 2002–2014. Treatments according to prevention guidelines, risks of coronary events, recurrent ischemic stroke, and major bleeding were assessed	In patients with stroke, risk of extracranial bleeds was higher in CVD patients (coronary and/or peripheral), especially in patients <75 years (8.1% vs 3.4%, $p = 0.005$; age- and sex-adjusted HR 2.71, 1.16–6.30), risk of intracerebral hemorrhage was not increased	60
3487 patients, 22.3% with ABI <0.9 (age 67 ± 11, 51% males), ABI ≥0.9 (age 64 ± 11, 58% males)	ABI measurement and assessment of stroke recurrence and risk of new vascular events after 24 months of follow-up	Low ABI increased risk for non-embolic ischemic stroke, transient ischemic attack, major vascular events and death (22.5% for ABI < 0.9 versus 13.7% for ABI ≥ 0.9; $p < 0.001$	61
48,094 acute coronary syndrome patients (mean age 64.0, IQ-range 56.6–72.0, 69% male), 8.5% with PAD (mean age 66.0, IQ-range 58.0–73.0, 73% male)	Analysis of 4 randomized trial data sets (PLATO, APPRAISE-2, TRA-CER, and TRILOGY ACS) on acute coronary syndrome for a follow-up period of 1 year	Patients with PAD had a higher risk of first and recurrent ischemic events after acute coronary syndrome, 14.3% vs 7.5% of major cardiovascular events, including stroke	62
231 symptomatic PAD patients (age	Patients performed a 4-m walk test, circulating inflammatory and	Higher levels of circulating biomarkers of inflammation and	63

(continued on next page)

Table 1 (*continued*)

Subjects	Study design	Main results	Ref
65 ± 10, 49% males)	vascular biomarkers were assessed and endothelial effects of circulating factors were characterized in a cell culture-based bioassay on primary human arterial endothelial cells	endothelial cell oxidative stress were associated with slower gait speed, slower cadence, and shorter stride length in older symptomatic patients with PAD. Previous cerebrovascular accidents increased risk to develop such gait impairments	
1069 diabetic patients (age 71.9; 63.6–78.0; 63% males)	Stroke severity and prognosis assessed from data of diabetic patients from 4 prospective ischaemic stroke registries (Acute Stroke Registry and Analysis of Lausanne (ASTRAL), Athens, Austrian, and Helsinki Stroke Thrombolysis Registries)	PAD in diabetic patients independently increased large-artery atherosclerotic stroke risk 4-fold (95% CI: 1.67–9.67)	64
Of 224 participants (age 70 ± 8, 40% males) 37 had an ABI ≤ 0.90 (age 75 ± 9, 19% males)	ABI determination and brain magnetic resonance imaging in stroke-free Atahualpa residents aged ≥60 years	ABI ≤ 0.9 was association with 3.72 (95% CI: 1.35–10.27) higher risk of lacunar infarcts	65
175 patients for coronary artery bypass surgery (mean age = 66.1, 71% males)	Extracranial Doppler duplex sonography, transcranial color-coded duplex sonography (TCCS) and transcranial Doppler (TCD) examination	PAD did not predict risk for intracranial artery stenosis	66
4299 subjects (age 45–75; 47.3% men) without previous stroke, CHD or myocardial infarcts	Subjects from the population-based Heinz Nixdorf Recall study were followed up for ischemic and hemorrhagic stroke events over 109.0 ± 23.3 months	Lower ABI (≤ 0.9) at baseline was associated with increased stroke compared to higher ABI (1.03 ± 0.22 vs. 1.13 ± 0.14, $p < 0.001$), especially at high Framingham risk score. ABI predicted stroke in addition to classical risk factors	67
Of 653 patients (age 69 (23–95), 67% males), 129 (age 72 (32–93), 65% males) had PAD	All 653 were patients with a first-ever acute ischemic stroke	Low ABI is a risk factor for stroke (HR 2.22, 95% CI 1.22–4.03) but 5-year risk of stroke recurrence was similar between low and normal ABI groups (HR 1.23, 95% CI 0.68–2.23)	68
538 Japanese type 2 diabetic patients (age 64 ± 11, 58% males), 9,7% with ABI <0.9	Prevalent silent cerebral infarction was assessed by cranial magnetic resonance imaging	The prevalence of silent cerebral infarction in patients with ABI < 0.9 was 88.5% (49.7% for those with ABI ≥ 0.9 and < 1.3 and 78.8% with ABI ≥ 1.3 ($p < 0.001$))	69
136 patients with symptomatic PAD (69.3 ± 9.9, 73% males) and 92 control participants without PAD (69.3 ± 11.6, 62% males)	Prevalence of cardiovascular risk factors, cerebral infarction, and cerebral white matter lesion (magnetic resonance imaging) and intracranial and extracranial carotid artery stenoses (magnetic resonance angiography)	More total cerebral infarctions in PAD patients (64.0% versus 29.0% in controls; $p < 0.001$). Advanced PAD (Fontaine III/IV) was associated with more symptomatic cerebral infarction and white matter lesions than in controls. More supraclinoid and cervical internal carotid artery stenoses in PAD patients (Fontaine IV)	70

ABI - ankle-brachial index, CHD - coronary heart disease, CI – confidence interval, CVD – cardiovascular disease, HR – hazard ratio, IC – intermittent claudication, IQ – interquartile, PAD – peripheral artery disease.

The present systematic literature review of the last decade on functional brain impairment in patients with PAD supports the deteriorating effect of PAD on cerebral capacities in agreement with previous assessment.[18,27] Cognitive performance was decreased in patients with PAD compared with their non-PAD peers.[56,71,73,74] Accordingly, it has been suggested to evaluate PAD risk with scores that take into account cerebral vascular disease.[84] Substantial cognitive decline leads to dementia and accordingly patients with dementia had a 2-fold frequency of previously undiagnosed PAD, compared to non-demented individuals.[75]

Adequate cerebral blood supply requires neurovascular coupling, which relies on endothelial function that is impaired in PAD. Owens and colleagues[71] demonstrated compromised microvascular endothelial function and neurovascular uncoupling in older patients with PAD and claudication, suggesting these endothelial dysfunctions to be involved in the development of associated impaired cognitive functions.

Importantly, exercise interventions that are efficient in treating primary PAD-related symptoms (pain and walking capacity) also improved cognitive capacities and QoL.[56,72] The role of exercise in PAD treatment and how exercise-mediated improvement in oxygen supply might benefit cognitive function is discussed in the next section.

Exercise to counteract PAD and cognitive dysfunction: improving oxygen supply

Exercise in PAD

Beside general CVD risk management (including other lifestyle measures and pharmacological/surgical strategies [for extensive reviews, see[5,85]]), exercise training is an important – but frequently not optimally used – pillar in PAD management and in the evaluation of disease progression.[5,86–91] Specifically, lower extremity functional performance is a useful mean to predict disease progression and mortality in patients with PAD.[92] These patients also have low average PA levels[93] and frequently severely reduced exercise capacity.[50,94] While a sedentary lifestyle is an independent risk factor to develop PAD,[12] the reduced ability of symptomatic patients with PAD to exercise might further aggravate disease progression. Therefore, regular exercise is a preventive strategy against PAD and supervised exercise therapy is recommended for patients with symptomatic PAD to reduce symptoms and improve overall functional status (i.e., walking performance) and QoL.[85,87,89,94–98] For example, the most recent published Cochrane review showed increased pain-free walking distance (82 m, 95% CI: 72 to 92 m; meta-analysis of 9 studies with 391 participants) and an improvement in maximal walking distance (120 m, 95% CI, 51 to 190 m; meta-analysis of 10 studies with 500 participants) after different exercise interventions compared to non-exercising controls.[97] Also, regular exercise training improves patients' awareness and compliance and reduces global cardiovascular risk.[85–87,95] Among the major physiological mechanisms of exercise benefits are improved lipid metabolism, improved oxidative metabolism in skeletal muscles, anti-inflammatory effects and possibly enhanced endothelial function and peripheral circulation.[90] Most exercise programs for patients with PAD are based on treadmill and track walking. For optimal benefits, exercise session should be performed for a minimum of 30–60 min, at least 3 times per week and for a minimum of 12 weeks [for extensive reviews, see[95] and[87]]. Although walking exercise is the most used training modality, it

Table 2
PAD Affects cognitive and psychological factors.

Subjects	Study design	Main results	Ref
11 symptomatic patients with PAD (age 63.7 ± 5.2, 6 males), 11 age- and sex-matched controls	Cognitive performance and functional near-infrared spectroscopy to assess neurovascular coupling responses during the cognitive *n*-back task. Peripheral microvascular endothelial function evaluated by laser speckle contrast imaging	Impaired visual memory, short-term memory, and attention in PAD patients. Impaired neurovascular coupling and peripheral microvascular endothelial function in PAD patients	[71]
138 patients (mean age 69.04 ± 10.94 years; 91.3% males)	Cross-sectional study using self-administered questionnaires: HRQOL (EQ-5D-5L) and a PAD-specific walking impairment questionnaire. Health behavior, social support, walking impairment, general health perceptions, and clinical characteristics were also measured	Patients' HRQOL (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) significantly associated with claudication pain, walking distance and stair climbing	[72]
58 symptomatic PAD patients (age: 69 ± 8 years) and 30 people without PAD but with other comorbid conditions (age: 62 ± 8 years) were compared	Neuropsychological tests to assess attention and working memory, verbal memory, non-verbal memory, perceptuo-motor speed, and executive function.	PAD patients had lower neuropsychological scores in all neuropsychological tests; worse test outcomes for PAD patients for attention, working memory, and verbal memory were independent of demographic characteristics and comorbidities	[56]
136 prevalent hemodialysis patients (age 59.3 ± 10.5, 56% male)	Cognitive performance measured by MoCA and CASI, linked to ABI (and brachial-ankle pulse wave velocity)	Hemodialysis patients with ABI < 0.9 had lower MoCA score ($p = 0.027$) and lower but not significant CASI scores ($p = 0.056$) compared to those with ABI > 0.9	[73]
130 patients (age 67 ± 8, 69% male)	Cognitive abilities assessed by MoCA and correlated with PA levels (total, light, and moderate-vigorous) obtained by an accelerometer.	Memory performance was higher if patients performed more moderate to vigorous PA ($p = 0.039$) and had better walking capacity ($p = 0.030$) after covariate adjustment	[21]
7991 participants (age 45–74, 44% males), without stroke or coronary heart disease	Cross-sectional data from the Hispanic Community Health Study/Study of Latinos, tests for verbal learning and memory, verbal fluency, executive function, and mental status (and composite global cognition)	Inverse u-shape association of continuous ABI with global cognition, verbal learning and memory, verbal fluency, executive function, but not with mental status	[74]
162 dementia patients age 78.87 ± 6.05 and 190 age- and gender-matched controls	ABI-based PAD diagnosis of people suffering or not from different types of dementia	The frequency of previously undetected PAD is more than twofold in patients with dementia (35.2%) compared to non-dementia controls (16.3%). Similar frequencies for Alzheimer's disease and vascular dementia	[75]
PAD patients grouped according to MMSE: 123 patients with perfect MMSE score (age 64 ± 10, 47% males); 123 with imperfect score (age 65 ± 11, 50% males)	Cognitive status (MMSE score) of 246 PAD patients was used to group patients. Characterization of walking (treadmill test), mobility, HRQOL (MOS SF-36)	Lower cognitive scores were associated with reducing walking capacities. Most associations of cognitive scores with dimensions of HRQOL were explained by comorbid conditions (coronary artery disease, chronic obstructive pulmonary disease, arthritis), only mental health was independently associated with cognitive scores	[20]
27 PAD (age 84.9 ± 8.4) and 22 non-PAD (age 83.4 ± 7.4) female patients	Comparison of daily living capacity between elderly women with and without PAD identification of factors related to this capacity	No differences of daily living capacity and of cognitive performance assessed by the MMSE between PAD and non-PAD	[76]
Of the 415 male non-demented patients with chronic coronary heart disease, 98 (age: 72 ± 6.9) had impaired and 317 (71.6 ± 5.9) had normal cerebrovascular reactivity	Patients were followed-up for 15 ± 3 years and assessed for cognitive function (Neurotrax Computerized Cognitive Battery) and for cerebrovascular reactivity using transcranial Doppler and for carotid plaques using ultrasound.	Cerebrovascular reactivity was more often impaired (6.2% versus 1.6%) in PAD patients. Impaired cerebrovascular reactivity overall was associated with worse cognitive function in male non-demented patients with chronic coronary heart disease	[77]
1601 sedentary adults without dementia (age 70–89, 33% males)	Baseline ABI and interviewer- and computer-administered cognitive function assessments; evaluation of a PA intervention. Cognitive function assessment also 18 or 30 months later	Low baseline ABI independently associated with worse cognitive function but not with overall changes in cognitive function test scores. Baseline ABI was associated with higher odds for 2-year progression to mild cognitive impairment or probable dementia (odds ratio 2.60 per unit lower ABI; 95% CI 1.06–6.37)	[78]
170 people of age 87 (47 with PAD, 54% males) and 748 people of age 73 (91 with PAD, 52% males)	Data from the Lothian Birth Cohort 1921 and 1936 studies. Nonverbal reasoning, verbal declarative memory, verbal fluency, working memory, and processing speed were assessed. Samples were screened for dementia. Controlled for age, sex, childhood mental ability, people with ABI >1.40 and/or history of cardiovascular or cerebrovascular disease excluded	No significant cognitive differences between persons with or without PAD, but a higher ABI was significantly associated with better general cognition and processing speed in the 87-year-old and better processing speed in the 73-year-old.	[79]
194 PAD patients (age 70.66 ± 9.44; 49% males)	6-month randomized controlled clinical trial. Home-based group-mediated cognitive behavioral walking	intervention versus control group: greater improvement on self-efficacy (p = 0.0008), satisfaction with	[80]

(*continued on next page*)

Table 2 (*continued*)

Subjects	Study design	Main results	Ref
	intervention (weekly group meeting, self-monitoring of walking exercise) versus attention control condition.	functioning (p = 0.0003), pain acceptance (p = 0.0002), and social functioning (p = 0.0008)	
153 patients after elective isolated coronary artery bypass graft surgery (age 72 ± 7; 71% males), 27 had PAD	magnetic resonance imaging and brain angiography, epiaortic ultrasound of the ascending aorta at the time of surgery, individual cognitive status and delirium were assessed	10.5% of overall patients had postoperative delirium, PAD (38% versus 15% in no PAD), preoperative decline in global cognitive function and pre-existing cerebral infarctions were risk factors to develop post-operative delirium	[81]

ABI - ankle-brachial index, CASI – Cognitive Abilities Screening Instrument, CI – confidence interval, HR – hazard ratio, HRQOL – Health-related quality of life, IC – intermittent claudication, MMSE – Mini-Mental State Examination, MoCA – Montreal Cognitive Assessment, PA – physical activity, PAD – peripheral artery disease.

has recently been shown that other non-walking training modes (arm-ergometer, resistance training, cycling) are also similarly effective.[99] Home-based exercise programs also showed effectiveness,[100] but induce lesser improvements compared to supervised programs.[101] A recent meta-analysis provides information on the effectiveness of various exercise modalities and on the objective (not pain-based) exercise intensities to improve treadmill performance in patients with PAD.[94] In this later study, walking at vigorous exercise intensity was most efficient to improve treadmill performance and maximal aerobic capacity (VO_{2max}) in these patients. Supervised exercise training not only enhances walking capacities and cardiorespiratory fitness of patients with PAD and claudication but is also associated with pronounced improvements of health-related QoL.[98,102,103] Wearable technologies and digital health-based strategies represent promising novel approaches to deliver supervised exercise training to patients at home[104] but improving the effectiveness of these interventions regarding both functional status and QoL, as well as their adherence rates, remain challenges for the future.[89,105]

Exercise benefits oxygen delivery to the brain

Physically active people (studied in individuals of 50 years or older) displayed a markedly reduced decline of cognitive functions (such as memory and verbal fluency) as compared to people with lower PA levels.[106] As discussed above, CVD risk factors increase the probability to develop dementia but the risk is mitigated by a healthy life style; for example as assessed by the Life's simple 7 score, a composite score of 7 modifiable health factors (smoking, body mass index, PA, diet, total cholesterol, blood pressure, and fasting blood glucose).[107] Regular PA benefits various cardiovascular parameters, including blood pressure and hemodynamics.[108] While it is well established that exercise ameliorates functional capacity and improves QoL in patients with PAD, less information is available for the potential of exercise to enhance cognitive functions or slow down cognitive decline in these patients. The most immediate effects of exercise are on skeletal muscle and include improved mitochondrial functions, metabolic adaptations, enhanced vasculature and muscle size regulation.[109,110] However, it is well established that exercise is also beneficial for other organs, including the heart and the brain.[53,111] Among the mediators of such systemic consequences of exercise are myokines/exerkines, which have also been suggested to be instrumental in cognitive exercise-induced improvements in PAD.[18] In addition, exercise-mediated microglial phenotype changes may be mechanisms of exercise-benefits on cognitive parameters in PAD.[18] Exercise further induces cellular responses that improve management of metabolism, oxidative stress and inflammation.[112]

PA can also improve blood vessels structurally and functionally not only in skeletal muscle but also peripherally, induces neovascularization and angiogenesis and in addition to cardiac benefits thus enhances overall perfusion.[110] Moreover, exercise has also been suggested to directly improve cerebrovascular capacities.[113] Mechanistically, these effects have been attributed to enhanced bioavailability of nitric oxide and improvement in endothelial function,[114] and to exercise-related shear stress and associated cellular and tissue adaptations.[113] PA furthermore ameliorates structural (stroke lesion size) and functional outcome after stroke, as shown in experimental and clinical studies.[114] Beside the discussed benefits of exercise on primary symptoms and cognition in patients with PAD, a correlation of mobility/gait impairments with cognitive deficits has been reported in symptomatic patients with PAD, suggesting cognitive testing as a potential screening tool for patients with poorer diagnosis.[20]

In summary, sufficient PA is beneficial in patients with PAD, including for their brain function. It is thus a highly synergistic strategy to counteract cognitive deficits linked to PAD. The effects of PA on systemic perfusion, vascular function also in the brain, optimization of oxygen-dependent reactions, as well as on protection of oxidative/inflammatory damage related to changes in oxygen availability likely are important mediators of these benefits. All these processes are compensatory mechanisms to improve oxygen supply, which are impaired in both PAD and many forms of dementias.

PAD- Related ischemia, exercise and the brain

Reduced limb perfusion in patients with PAD leads to muscle ischemia and consequently to reduced oxygen and glucose availability; and in this context can have detrimental effects. Conversely, ischemic conditioning - the application of mild/sub-harmful periods of ischemia-reperfusion - protects cells and tissues from subsequent severe ischemia-reperfusion. Exercise can also represent an ischemic challenge by changing systemic perfusion. Accordingly, ischemic conditioning has been suggested to partially mediate beneficial effects of exercise on claudication symptoms and exercise capacity improvement.[115] Mechanistically conditioning effects depend on molecular events like the upregulation of cellular anti-oxidative capacities (importantly orchestrated by nuclear factor-E2-related factor (Nrf2)) and the induction of the unfolded protein response (UPR), a response to deficits in proteostasis following for example hypoxic or ischemic insults.[116] Treadmill training in patients with PAD not only improved pain-free walking distance but was associated with similar molecular processes in peripheral blood mononuclear cells (PBMCs) as would be expected from ischemic conditioning.[117] These authors observed an up-regulation of Nrf2 and UPR in PBMCs, leading to increased levels of the antioxidative enzyme glutathione in plasma. In PBMCs, they recorded reduced oxidative stress and improved cell viability. These effects suggest that treadmill exercise might trigger conditioning comparable to mild ischemic stimuli.

A normal response of healthy individuals to limb ischemia is an upregulation of angiogenesis and the coordination of vascular remodeling and defenses against oxidative stress and inflammation (referred to as conditioning, if the ischemic challenge is sub-harmful), processes that fail in critical limb ischemia.[118] Ongoing unrestrained oxidative and inflammatory strain and insufficient tissue perfusion lead to mitochondrial, cell and tissue damage. Several circulating molecular factors associated with these alterations may be useful biomarkers for diagnosis, assessment of disease progression and prognosis of PAD.[118] These authors highlight the challenges in finding specific biomarkers of PAD that can differentiate between PAD and other diseases with atherothrombotic components.

Transient ischemic episodes outside of the brain and subsequent

impaired peripheral blood supply and oxygen delivery can induce a phenomenon termed remote ischemic conditioning that can mitigate infarct size and functional outcomes of ischemic stroke. While PAD is associated with increased risk to experience stroke, it has been hypothesized that the impaired oxygen supply in PAD may represent remote ischemic conditioning by itself and mitigate outcomes. This mechanism is in line with the suggestion that PAD could be a protective factor on stroke volume and deleterious outcomes.[119] This report, however, is not in agreement with other studies showing worse outcomes of stroke in people with lower ABI (e.g.[120]). Furthermore, a recent study on acute stroke patients with or without PAD, who all had undergone endovascular thrombectomy, did not find differences in functional, structural (collateral scores) or safety outcomes.[121] Therefore, although PAD leads to peripheral ischemia, its chronic nature and the potentially impaired adaptive capacities to ischemia in PAD[118] in most cases likely result in unfavorable outcomes, including on the brain.

Improving oxygen supply to the brain in PAD

Beyond the discussed potential of exercise to indirectly improve oxygen supply in the brain of patients with PAD, other strategies can be envisioned to impact oxygen supply more directly. These possibilities may be especially important as complementary ways to improve oxygen availability in the brain of patients with PAD with severely impaired exercise capacity.

Pharmacological and genetic modulation of oxygen supply in PAD

The phosphodiesterase III inhibitor cilostazol inhibits platelet function and improves vascular endothelial function[122] and is a widely used drug to treat intermittent claudication in PAD. Cilostazol further improves cognitive dysfunction induced by beta-amyloid aggregation in mouse models of Alzheimer's disease[123,124] and after ischemic stroke in humans.[125] Therefore, it may be a particularly suitable drug to treat patients with PAD with cognitive impairment.

Another way of inducing molecular responses leading to increased oxygen supply, is the stabilization of HIFs (see above) or the upregulation of its transcriptional targets. Many related approaches have been explored already as treatment strategies in PAD. For instance, HIF-stabilization (via deletion of prolyl-hydroxylases 1 and 3), improved perfusion and motor function recovery in PAD-model mice (hind-limb ischemia model).[126] Similarly, blood flow recovery and neovascularization were enhanced following gene silencing of prolyl-hydroxylase 2 and subsequent HIF-1 upregulation in hind-limb ischemia model mice.[127] On the other hand, stabilizing HIFs using a compound to inhibit HIF-prolyl-hydroxylase, GSK1278863, (and thereby inhibiting HIF degradation) did not improve PAD-related symptoms in patients at the used concentrations (300 mg single dose and 15 mg daily for 14 days).[128] Importantly, in this study, no upregulation of HIF target genes in calf-muscle biopsies were observed, casting doubt on successful target engagement of the applied regimens.

To directly modulate expression levels of HIFs, several gene-therapy approaches for PAD are based on the overexpression of the oxygen-level regulated HIF-1 subunit HIF-1alpha[129] or HIF target genes encoding vascular endothelial growth factor (VEGF), as summarized in a recent systematic review.[130] However, no clear and reliable benefits for primary PAD symptoms were reported in these studies.[130] Whether such approaches benefit cognitive decline in these patients or whether the treatment regimens have still to be optimized, merits further scrutiny.

Levels of HIF-regulated heme oxygenases (heat shock proteins regulating oxidative stress) have been shown to correlate positively with PAD severity; but, whether this is an adaptive response or a pathology-driving factor is not well understood.[131] Strategies of pharmacological modulation of heme oxygenases are also considered future avenues for treatments of both PAD and cerebrovascular diseases.[131]

Another treatment strategy in PAD is based on the use of stem cells. Interestingly, HIFs and their target genes appear to also be important factors for the efficiency of such interventions. For example, HIF-overexpression in cardiac stem cells improved their survival and effectivity of proangiogenic factor production during subsequent transplantation in a mouse hind-limb ischemia model.[132] The treatment improved blood flow and tissue repair in those mice. Also, higher levels of VEGF secreted from transplanted VEGF- overexpressing mesenchymal stromal cells have been demonstrated to support angiogenesis in a mouse model of hind limb ischemia, suggesting the potential usefulness of similar approaches for PAD.[133]

Given the role of HIFs in disease development and progression and the potential of HIF modulation in neurological diseases,[38,39,45,46] strategies to improve HIF-signaling in PAD may also yield cognitive benefits. However, the current experimental knowledge on this association is poor and needs to be scientifically explored.

Potential of hypoxia conditioning for PAD symptoms and cognitive consequences

Therapies that modulate oxygen levels are potential beneficial interventions for PAD. For example, topical oxygen therapy (local application of 100% oxygen at atmospheric pressure) has been shown to improve wound healing in patients with PAD.[134] This is not surprising, since hyperbaric oxygen therapy is a well-established therapy for ischemic wound healing in general.[135,136] This treatment has also been demonstrated to improve antioxidant defenses and mitigate atherosclerosis formation in rabbits[137] and it ameliorated blood perfusion and muscle regeneration in experimental hind-limb ischemia in mice.[138] More recently, hyperbaric oxygen therapy in patients with PAD has been demonstrated to improve blood flow in ischemic areas and to elevate circulating levels of endothelial progenitor cells and angiogenesis biomarkers (including vascular endothelial growth factor and fibroblast growth factor).[139] However, despite these potential benefits, hyperbaric oxygen therapy is not considered a valuable tool to treat chronic limb threatening ischemia.[140]

The benefits of hyperbaric oxygen therapy in wound healing rely partially on the activation of HIF-pathways.[141] The paradoxical stabilization of HIF also at high oxygen levels has been described previously[142] and raises the question, whether intermittent hypoxia conditioning (i.e., the repeated short-term application of mild hypoxia for therapeutic purposes) may not yield more direct benefits in PAD. Intermittent hypoxia can substantially modulate vessel structure and function.[143] While this can be detrimental in the case of uncontrolled hypoxia exposure, it highlights the potential of well-calibrated exposures to hypoxia as an interventional strategy to induce beneficial adaptations of the vasculature to better tolerate PAD-related conditions of impaired oxygen delivery. Controlled exposure to hypoxia indeed represents a means to improve cardiovascular function[144,145] and concurrently has shown benefit in the treatment of brain-related diseases, for example in the common dementia-prodrome mild cognitive impairment, as recently reviewed.[44,146] In contrast to hyperoxic strategies, which aim to acutely rescue reduced oxygenation but not necessarily induce long-term benefits, hypoxia conditioning is based on the principle of hormesis. According to this principle, a mild stressor, such as mild hypoxia, can induce protective effects to subsequent more dangerous stressors; e.g., severe hypoxia or ischemia.[142] The mild hypoxic stress thereby is thought to - beside structural and functional adaptations of vessels - induce metabolic reprogramming and the upregulation of molecular factors that can limit oxidative stress and inflammation, all processes importantly mediated by HIFs.[142] Together, these responses contribute to a better tolerance of hypoxia and cyto- and tissue-protection, via reduced reliance on oxygen, improved blood (and oxygen) supply and molecular and biochemical protection from damage caused by both hypoxia and subsequent reperfusion.

While not yet extensively explored in the context of PAD, based on its beneficial effects on cardiovascular and brain function, hypoxia

conditioning may be an efficient treatment strategy for cognitive decline in PAD and other PAD symptoms. Exposure to very mild simulated altitude (corresponding to about 1700 m) has already been shown to be beneficial in rodent PAD models by improving blood perfusion.[147]

Conclusions

Deficits in vascular function in PAD have consequences on the oxygen supply not only in peripheral tissues but also in the brain. Impaired oxygen supply in the brain is associated with an increased vulnerability for brain damage and deteriorating cognitive functions; outcomes that are commonly observed in patients with PAD. Improving systemic oxygen supply, for example by exercise, therefore does not only ameliorate limb symptoms in PAD as a great body of evidence suggests but has the potential to also mitigate deleterious effects on the brain. That the enhancement of systemic oxygen delivery mechanisms reduces PAD symptoms and associated brain deficits is further supported by preclinical evidence showing benefits of pharmacological or genetic modulation of core molecular factors in the adaptation to variations in oxygen availability, such as HIFs and its target gene products. The lack of success to translate these preclinical results to patients with PAD may indicate a yet insufficient understanding of the intricate regulation of natural processes to counterbalance and adapt to oxygen availability abnormalities (i.e., hypoxia or hyperoxia). The induction or modulation of endogenous adaptations to oxygen level variations, more specific than exercise but less specific than pharmacological or genetic approaches, may represent a promising strategy to achieve increased resilience to PAD and associated cognitive symptoms. Protocols that vary the concentration of available oxygen, such as intermittent hypoxia conditioning, hyperbaric oxygen therapy or combinations thereof[146] and that can be applied during exercise or during rest (especially important for patients with impaired exercise capacity or exercise induced pain) merit further consideration as preventive or interventional approaches for PAD-related cognitive decline.

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Credit author statement

JB and MP conceived the idea for the manuscript. JB drafted the first version of the manuscript and created the visualization. GPM, MF, SL, LM and MP reviewed and edited the manuscript. JB and MP supervised and coordinated the manuscript finalization. All authors have read and agreed to the final version of the manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest.

References

1. Shu J, Santulli G. Update on peripheral artery disease: epidemiology and evidence-based facts. *Atherosclerosis.* 2018;275:379–381.
2. Leeper NJ, Kullo IJ, Cooke JP. Genetics of peripheral artery disease. *Circulation.* 2012;125:3220–3228.
3. Rontoyanni VG, Nunez Lopez O, Fankhauser GT, Cheema ZF, Rasmussen BB, Porter C. Mitochondrial bioenergetics in the metabolic myopathy accompanying peripheral artery disease. *Front Physiol.* 2017;8:141.
4. Lau JF, Weinberg MD, Olin JW. Peripheral artery disease. Part 1: clinical evaluation and noninvasive diagnosis. *Nat Rev Cardiol.* 2011;8:405–418.
5. Shamaki GR, Markson F, Soji-Ayoade D, Agwuegbo CC, Bamgbose MO, Tamunoinemi BM. Peripheral artery disease: a comprehensive updated review. *Curr Probl Cardiol.* 2021:101082.
6. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet (London, England).* 2013;382:1329–1340.
7. Song P, Fang Z, Wang H, et al. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. *Lancet Glob Health.* 2020;8:e721–e729.
8. Aday AW, Matsushita K. Epidemiology of peripheral artery disease and polyvascular disease. *Circ Res.* 2021;128:1818–1832.
9. Scully RE, Arnaoutakis DJ, DeBord Smith A, Semel M, Nguyen LL. Estimated annual health care expenditures in individuals with peripheral arterial disease. *J Vasc Surg.* 2018;67:558–567.
10. Meijer WT, Grobbee DE, Hunink MG, Hofman A, Hoes AW. Determinants of peripheral arterial disease in the elderly: the Rotterdam study. *Arch Intern Med.* 2000;160:2934–2938.
11. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *Eur J Vasc Endovasc Surg.* 2007;33(suppl 1):S1–75.
12. Wilson AM, Sadrzadeh-Rafie AH, Myers J, et al. Low lifetime recreational activity is a risk factor for peripheral arterial disease. *J Vasc Surg.* 2011;54(427–432), 432. e421–424.
13. McDermott MM, Guralnik JM, Ferrucci L, et al. Asymptomatic peripheral arterial disease is associated with more adverse lower extremity characteristics than intermittent claudication. *Circulation.* 2008;117:2484–2491.
14. McDermott MM, Fried L, Simonsick E, Ling S, Guralnik JM. Asymptomatic peripheral arterial disease is independently associated with impaired lower extremity functioning: the women's health and aging study. *Circulation.* 2000;101:1007–1012.
15. Behroozian AA, Beckman JA. Asymptomatic peripheral artery disease: silent but deadly. *Prog Cardiovasc Dis.* 2021;65:2–8.
16. Polonsky TS, McDermott MM. Lower extremity peripheral artery disease without chronic limb-threatening ischemia: a review. *Jama.* 2021;325:2188–2198.
17. Waldstein SR, Tankard CF, Maier KJ, et al. Peripheral arterial disease and cognitive function. *Psychosom Med.* 2003;65:757–763.
18. Leardini-Tristao M, Charles AL, Lejay A, et al. Beneficial effect of exercise on cognitive function during peripheral arterial disease: potential involvement of myokines and microglial anti-inflammatory phenotype enhancement. *J Clin Med.* 2019:8.
19. Rafnsson SB, Deary IJ, Fowkes FG. Peripheral arterial disease and cognitive function. *Vasc Med.* 2009;14:51–61.
20. Gardner AW, Waldstein SR, Montgomery PS, Zhao YD. Effect of cognitive status on exercise performance and quality of life in patients with symptomatic peripheral artery disease. *J Vasc Surg.* 2016;63:98–104.
21. Cavalcante BR, Germano-Soares AH, Gerage AM, et al. Association between physical activity and walking capacity with cognitive function in peripheral artery disease patients. *Eur J Vasc Endovasc Surg.* 2018;55:672–678.
22. Krock BL, Skuli N, Simon MC. Hypoxia-induced angiogenesis: good and evil. *Genes Cancer.* 2011;2:1117–1133.
23. Heald CL, Fowkes FG, Murray GD, Price JF. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. *Atherosclerosis.* 2006;189:61–69.
24. Breteler MM, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam Study. *Bmj.* 1994;308:1604–1608.
25. Hofman A, Ott A, Breteler MM, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet.* 1997;349:151–154.
26. Newman AB, Fitzpatrick AL, Lopez O, et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the cardiovascular health study cohort. *J Am Geriatr Soc.* 2005;53:1101–1107.
27. Guerchet M, Aboyans V, Nubukpo P, Lacroix P, Clément JP, Preux PM. Ankle-brachial index as a marker of cognitive impairment and dementia in general population. A systematic review. *Atherosclerosis.* 2011;216:251–257.
28. Laurin D, Masaki KH, White LR, Launer LJ. Ankle-to-brachial index and dementia: the Honolulu-Asia aging study. *Circulation.* 2007;116:2269–2274.
29. de la Torre JC, Stefano GB. Evidence that Alzheimer's disease is a microvascular disorder: the role of constitutive nitric oxide. *Brain Res Brain Res Rev.* 2000;34:119–136.
30. de la Torre JC. Alzheimer disease as a vascular disorder: nosological evidence. *Stroke.* 2002;33:1152–1162.
31. Karimi N, Haghani M, Noorafshan A, Moosavi SMS. Structural and functional disorders of hippocampus following ischemia/reperfusion in lower limbs and kidneys. *Neuroscience.* 2017;358:238–248.
32. Chen Y, Zhou J, Li J, et al. Electroacupuncture pretreatment prevents cognitive impairment induced by limb ischemia-reperfusion via inhibition of microglial activation and attenuation of oxidative stress in rats. *Brain Res.* 2012;1432:36–45.
33. Burtscher J, Maglione V, Di Pardo A, Millet GP, Schwarzer C, Zangrandi L. A rationale for hypoxic and chemical conditioning in Huntington's disease. *Int J Mol Sci.* 2021;22.
34. Burtscher J, Syed MMK, Keller MA, Lashuel HA, Millet GP. Fatal attraction - the role of hypoxia when alpha-synuclein gets intimate with mitochondria. *Neurobiol Aging.* 2021;107:128–141.
35. Burtscher J, Syed MMK, Lashuel HA, Millet GP. Hypoxia conditioning as a promising therapeutic target in Parkinson's disease? *Mov Disord.* 2021;36:857–861.

36. Serebrovskaya T, Karaban I, Mankovskaya I, Bernardi L, Passino C, Appenzeller O. Hypoxic ventilatory responses and gas exchange in patients with Parkinson's disease. *Resp Int Rev Thoracic Dis*. 1998;65:28–33.
37. Onodera H, Okabe S, Kikuchi Y, Tsuda T, Itoyama Y. Impaired chemosensitivity and perception of dyspnoea in Parkinson's disease. *Lancet*. 2000;356:739–740.
38. Burtscher J, Mallet RT, Burtscher M, Millet GP. Hypoxia and brain aging: neurodegeneration or neuroprotection? *Ageing Res Rev*. 2021;68, 101343.
39. March-Diaz R, Lara-Ureña N, Romero-Molina C, et al. Hypoxia compromises the mitochondrial metabolism of Alzheimer's disease microglia via HIF1. *Nat Aging*. 2021;1:385–399.
40. Zhang X, Le W. Pathological role of hypoxia in Alzheimer's disease. *Exp Neurol*. 2010;223:299–303.
41. Alvarez-Vergara MI, Rosales-Nieves AE, March-Diaz R, et al. Non-productive angiogenesis disassembles Aß plaque-associated blood vessels. *Nat Commun*. 2021; 12:3098.
42. Kaelin Jr WG, Ratcliffe PJ. Oxygen sensing by metazoans: the central role of the HIF hydroxylase pathway. *Mol Cell*. 2008;30:393–402.
43. Gao L, Chen Q, Zhou X, Fan L. The role of hypoxia-inducible factor 1 in atherosclerosis. *J Clin Pathol*. 2012;65:872–876.
44. Burtscher J, Mallet RT, Burtscher M, Millet GP. Hypoxia and brain aging: neurodegeneration or neuroprotection? *Ageing Res Rev*. 2021;68, 101343.
45. Correia SC, Moreira PI. Oxygen sensing and signaling in Alzheimer's disease: a breathtaking story!. *Cell Mol Neurobiol*. 2021;42:3–21.
46. Correia SC, Carvalho C, Cardoso S, et al. Defective HIF signaling pathway and brain response to hypoxia in neurodegenerative diseases: not an "iffy" question!. *Curr Pharm Des*. 2013;19:6809–6822.
47. Klarin D, Lynch J, Aragam K, et al. Genome-wide association study of peripheral artery disease in the million veteran program. *Nat Med*. 2019;25:1274–1279.
48. Gratl A, Wipper S, Frese JP, Raude B, Greiner A, Pesta D. The role of mitochondrial function in peripheral arterial disease: insights from translational studies. *Int J Mol Sci*. 2021:22.
49. Pizzimenti M, Riou M, Charles A-L, et al. The rise of mitochondria in peripheral arterial disease physiopathology: experimental and clinical data. *J Clin Med*. 2019; 8:2125.
50. Hiatt WR, Nawaz D, Brass EP. Carnitine metabolism during exercise in patients with peripheral vascular disease. *J Appl Physiol*. 1985;1987(62):2383–2387.
51. Gratl A, Pesta D, Gruber L, et al. The effect of revascularization on recovery of mitochondrial respiration in peripheral artery disease: a case control study. *J Transl Med*. 2021;19:244.
52. Gratl A, Frese J, Speichinger F, et al. Regeneration of mitochondrial function in gastrocnemius muscle in peripheral arterial disease after successful revascularisation. *Eur J Vasc Endovasc Surg*. 2020;59:109–115.
53. Burtscher J, Millet GP, Place N, Kayser B, Zanou N. The muscle-brain Axis and neurodegenerative diseases: the key role of mitochondria in exercise-induced neuroprotection. *Int J Mol Sci*. 2021;22:6479.
54. Monzio Compagnoni G, Di Fonzo A, Corti S, Comi GP, Bresolin N, Masliah E. The role of mitochondria in neurodegenerative diseases: the lesson from Alzheimer's disease and Parkinson's disease. *Mol Neurobiol*. 2020;57:2959–2980.
55. Stefanidis KB, Askew CD, Greaves K, Summers MJ. The effect of non-stroke cardiovascular disease states on risk for cognitive decline and dementia: a systematic and Meta-analytic review. *Neuropsychol Rev*. 2018;28:1–15.
56. Gardner AW, Montgomery PS, Wang M, et al. Cognitive decrement in older adults with symptomatic peripheral artery disease. *Geroscience*. 2021;43:2455–2465.
57. Bhatt SK, Tseng AS, Firth C, et al. Abnormal vascular physiology in the lower extremities as a risk factor for ischemic stroke and mortality. *J Osteopath Med*. 2021;121:463–470.
58. Virtanen J, Varpela M, Biancari F, Jalkanen J, Hakovirta H. Association between anatomical distribution of symptomatic peripheral artery disease and cerebrovascular disease. *Vascular*. 2020;28:295–300.
59. Shin YY, Ha SH, Woo HG, Heo SH, Chang DI, Kim BJ. Subclinical peripheral arterial disease in patients with acute ischemic stroke: a study with ultrasonography. *J Stroke Cerebrovasc Dis*. 2019;28, 104370.
60. Boulanger M, Li L, Lyons S, et al. Effect of coexisting vascular disease on long-term risk of recurrent events after TIA or stroke. *Neurology*. 2019;93:e695–e707.
61. Abboud H, Monteiro Tavares L, Labreuche J, et al. Impact of low ankle-brachial index on the risk of recurrent vascular events. *Stroke*. 2019;50:853–858.
62. Inohara T, Pieper K, Wojdyla DM, et al. Incidence, timing, and type of first and recurrent ischemic events in patients with and without peripheral artery disease after an acute coronary syndrome. *Am Heart J*. 2018;201:25–32.
63. Gardner AW, Montgomery PS, Casanegra AI, Silva-Palacios F, Ungvari Z, Csiszar A. Association between gait characteristics and endothelial oxidative stress and inflammation in patients with symptomatic peripheral artery disease. *Age (Dordr)*. 2016;38:64.
64. Ntaios G, Milionis H, Vemmos K, et al. Small-vessel occlusion versus large-artery atherosclerotic strokes in diabetics: patient characteristics, outcomes, and predictors of stroke mechanism. *Eur Stroke J*. 2016;1:108–113.
65. Del Brutto OH, Sedler MJ, Mera RM, et al. The association of ankle-brachial index with silent cerebral small vessel disease: results of the Atahualpa Project. *Int J Stroke*. 2015;10:589–593.
66. Luchowski P, Wojczal J, Buraczynska K, Kozlowicz M, Stazka J, Rejdak K. Predictors of intracranial cerebral artery stenosis in patients before cardiac surgery and its impact on perioperative and long-term stroke risk. *Neurol Neurochir Pol*. 2015;49:395–400.
67. Gronewold J, Hermann DM, Lehmann N, et al. Ankle-brachial index predicts stroke in the general population in addition to classical risk factors. *Atherosclerosis*. 2014; 233:545–550.
68. Milionis H, Vemmou A, Ntaios G, et al. Ankle-brachial index long-term outcome after first-ever ischaemic stroke. *Eur J Neurol*. 2013;20:1471–1478.
69. Bouchi R, Babazono T, Takagi M, et al. Non-linear association between ankle-brachial pressure index and prevalence of silent cerebral infarction in Japanese patients with type 2 diabetes. *Atherosclerosis*. 2012;222:490–494.
70. Aizawa H, Azuma N, Katayama T, et al. Cerebrovascular disease and intracranial artery stenosis in patients with symptomatic peripheral artery disease. *J Stroke Cerebrovasc Dis*. 2012;21:825–831.
71. Owens CD, Mukli P, Csipo T, et al. Microvascular dysfunction and neurovascular uncoupling are exacerbated in peripheral artery disease, increasing the risk of cognitive decline in older adults. *Am J Physiol Heart Circ Physiol*. 2022;322: H924–h935.
72. Kim M, Kim Y, Ryu GW, Choi M. Functional status and health-related quality of life in patients with peripheral artery disease: a cross-sectional study. *Int J Environ Res Public Health*. 2021:18.
73. Wu PH, Lin YT, Wu PY, et al. A low ankle-brachial index and high brachial-ankle pulse wave velocity are associated with poor cognitive function in patients undergoing hemodialysis. *Dis Markers*. 2019;2019:9421352.
74. Tarraf W, Criqui MH, Allison MA, et al. Ankle brachial index and cognitive function among Hispanics/Latinos: results from the Hispanic community health study/study of Latinos. *Atherosclerosis*. 2018;271:61–69.
75. Tasci I, Safer U, Naharci MI, et al. Undetected peripheral arterial disease among older adults with Alzheimer's disease and other dementias. *Am J Alzheimers Dis Other Dement*. 2018;33:5–11.
76. Cucato GG, Ritti-Dias RM, Franco FG, et al. Influence of peripheral arterial disease on daily living activities in elderly women. *J Vasc Nurs*. 2016;34:39–43.
77. Haratz S, Weinstein G, Molshazki N, et al. Impaired cerebral hemodynamics and cognitive performance in patients with Atherothrombotic disease. *J Alzheimers Dis*. 2015;46:137–144.
78. Espeland MA, Newman AB, Sink K, et al. Associations between ankle-brachial index and cognitive function: results from the lifestyle interventions and Independence for elders trial. *J Am Med Dir Assoc*. 2015;16:682–689.
79. Laukka EJ, Starr JM, Deary IJ. Lower ankle-brachial index is related to worse cognitive performance in old age. *Neuropsychology*. 2014;28:281–289.
80. Rejeski WJ, Spring B, Domanchuk K, et al. A group-mediated, home-based physical activity intervention for patients with peripheral artery disease: effects on social and psychological function. *J Transl Med*. 2014;12:29.
81. Otomo S, Maekawa K, Goto T, Baba T, Yoshitake A. Pre-existing cerebral infarcts as a risk factor for delirium after coronary artery bypass graft surgery. *Interact Cardiovasc Thorac Surg*. 2013;17:799–804.
82. Slark J, Bentley P, Sharma P. Silent brain infarction in the presence of systemic vascular disease. *JRSM. Cardiovasc Dis*. 2012:1.
83. Banerjee A, Fowkes FG, Rothwell PM. Associations between peripheral artery disease and ischemic stroke: implications for primary and secondary prevention. *Stroke*. 2010;41:2102–2107.
84. Wu KL, Kuo CY, Tsai YC, et al. $CHADS_2$, CHA_2DS_2ASc, and new ABCD scores predict the risk of peripheral arterial disease in patients with sleep apnea. *J Clin Med*. 2019:8.
85. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2017;69:e71–e126.
86. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European stroke organization (ESO)the task force for the diagnosis and treatment of peripheral arterial diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J*. 2018;39:763–816.
87. Treat-Jacobson D, McDermott MM, Bronas UG, et al. Optimal exercise programs for patients with peripheral artery disease: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e10–e33.
88. Suriben R, Chen M, Higbee J, et al. Antibody-mediated inhibition of GDF15-GFRAL activity reverses cancer cachexia in mice. *Nat Med*. 2020;26:1264–1270.
89. Khoury SR, Ratchford EV, Stewart KJ. Supervised exercise therapy for patients with peripheral artery disease: clinical update and pathways forward. *Prog Cardiovasc Dis*. 2022;70:183–189.
90. Hallak AO, Hallak FZ, Hallak YO, et al. Exercise therapy in the management of peripheral arterial disease. *Mayo Clin Proc Innov Qual Outcomes*. 2023;7:476–489.
91. Krittanawong C, Escobar J, Virk HUH, et al. Lifestyle approach and medical therapy of lower extremity peripheral artery disease. *Am J Med*. 2023. online ahead of print.
92. Morris DR, Rodriguez AJ, Moxon JV, et al. Association of lower extremity performance with cardiovascular and all-cause mortality in patients with peripheral artery disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2014:3.
93. McDermott MM, Greenland P, Ferrucci L, et al. Lower extremity performance is associated with daily life physical activity in individuals with and without peripheral arterial disease. *J Am Geriatr Soc*. 2002;50:247–255.
94. Fassora M, Calanca L, Jaques C, Mazzolai L, Kayser B, Lanzi S. Intensity-dependent effects of exercise therapy on walking performance and aerobic fitness in symptomatic patients with lower-extremity peripheral artery disease: a systematic review and meta-analysis. *Vasc Med*. 2022;27:158–170.

95. Harwood AE, Pymer S, Ingle L, et al. Exercise training for intermittent claudication: a narrative review and summary of guidelines for practitioners. *BMJ Open Sport Exerc Med*. 2020;6, e000897.
96. Fakhry F, van de Luijtgaarden KM, Bax L, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg*. 2012;56:1132–1142.
97. Lane R, Harwood A, Watson L, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2017;12, Cd000990.
98. Parmenter BJ, Dieberg G, Phipps G, Smart NA. Exercise training for health-related quality of life in peripheral artery disease: a systematic review and meta-analysis. *Vasc Med*. 2015;20:30–40.
99. Jansen SC, Abaraogu UO, Lauret GJ, Fakhry F, Fokkenrood HJ, Teijink JA. Modes of exercise training for intermittent claudication. *Cochrane Database Syst Rev*. 2020;8, Cd009638.
100. McDermott MM. Medical management of functional impairment in peripheral artery disease: a review. *Prog Cardiovasc Dis*. 2018;60:586–592.
101. Pymer S, Ibeggazene S, Palmer J, et al. An updated systematic review and meta-analysis of home-based exercise programs for individuals with intermittent claudication. *J Vasc Surg*. 2021;74:2076–2085.e2020.
102. Lanzi S, Calanca L, Berchtold A, Mazzolai L. Improvement in 6-minute walking distance after supervised exercise training is related to changes in quality of life in patients with lower extremity peripheral artery disease. *J Clin Med*. 2021:10.
103. Novaković M, Krevel B, Rajkovič U, et al. Moderate-pain versus pain-free exercise, walking capacity, and cardiovascular health in patients with peripheral artery disease. *J Vasc Surg*. 2019;70:148–156.
104. Kim Y, Kim M, Ryu GW, Choi M. Development of home-based exercise Mobile application for patients with peripheral artery disease. *Stud Health Technol Inform*. 2021;284:359–361.
105. Kim M, Kim C, Kim E, Choi M. Effectiveness of Mobile health-based exercise interventions for patients with peripheral artery disease: systematic review and Meta-analysis. *JMIR Mhealth Uhealth*. 2021;9, e24080.
106. Cheval B, Csajbók Z, Formánek T, et al. Association between physical-activity trajectories and cognitive decline in adults 50 years of age or older. *Epidemiol Psychiatr Sci*. 2021:30.
107. Tin A, Bressler J, Simino J, et al. Genetic risk, midlife life's simple 7, and incident dementia in the atherosclerosis risk in communities study. *Neurology*. 2022;99:e154–e163.
108. Zócalo Y, Gómez-García M, Torrado J, Bia D. Aging-related moderation of the link between compliance with international physical activity recommendations and the hemodynamic, structural, and functional arterial status of 3,619 subjects aged 3-90 years. *Front Sports Active Living*. 2022;4:800249.
109. Hood DA, Memme JM, Oliveira AN, Triolo M. Maintenance of skeletal muscle mitochondria in health, exercise, and aging. *Annu Rev Physiol*. 2019;81:19–41.
110. Pinckard K, Baskin KK, Stanford KI. Effects of exercise to improve cardiovascular health. *Front Cardiovasc Med*. 2019;6:69.
111. Burtscher J, Soltany A, Visavadiya NP, et al. Mitochondrial stress and mitokines in aging. *Aging Cell*. 2023;22, e13770.
112. Burtscher J, Burtscher M, Millet GP. The central role of mitochondrial fitness on antiviral defenses: an advocacy for physical activity during the COVID-19 pandemic. *Redox Biol*. 2021;43, 101976.
113. Calverley TA, Ogoh S, Marley CJ, et al. HIITing the brain with exercise: mechanisms, consequences and practical recommendations. *J Physiol*. 2020;598:2513–2530.
114. Schmidt W, Endres M, Dimeo F, Jungehulsing GJ. Train the vessel, gain the brain: physical activity and vessel function and the impact on stroke prevention and outcome in cerebrovascular disease. *Cerebrovasc Dis*. 2013;35:303–312.
115. Ahmed KMT, Hernon S, Mohamed S, Tubassum M, Newell M, Walsh SR. Remote ischemic pre-conditioning in the management of intermittent claudication: a pilot randomized controlled trial. *Ann Vasc Surg*. 2019;55:122–130.
116. Burtscher J, Romani M, Bernardo G, et al. Boosting mitochondrial health to counteract neurodegeneration. *Prog Neurobiol*. 2022;215, 102289.
117. Fratta Pasini AM, Stranieri C, Rigoni AM, et al. Physical exercise reduces cytotoxicity and up-regulates Nrf2 and UPR expression in circulating cells of peripheral artery disease patients: an hypoxic adaptation? *J Atheroscler Thromb*. 2018;25:808–820.
118. Krishna SM, Moxon JV, Golledge J. A review of the pathophysiology and potential biomarkers for peripheral artery disease. *Int J Mol Sci*. 2015;16:11294–11322.
119. Connolly M, Bilgin-Freiert A, Ellingson B, et al. Peripheral vascular disease as remote ischemic preconditioning, for acute stroke. *Clin Neurol Neurosurg*. 2013;115:2124–2129.
120. Kim J, Lee DH, Cha MJ, et al. Low ankle-brachial index is an independent predictor of poor functional outcome in acute cerebral infarction. *Atherosclerosis*. 2012;224:113–117.
121. Pirson FAV, Hinsenveld WH, Staals J, et al. Peripheral artery disease in acute ischemic stroke patients treated with endovascular thrombectomy; results from the MR CLEAN registry. *Front Neurol*. 2020;11, 560300.
122. Goto S. Cilostazol: potential mechanism of action for antithrombotic effects accompanied by a low rate of bleeding. *Atheroscler Suppl*. 2005;6:3–11.
123. Hiramatsu M, Takiguchi O, Nishiyama A, Mori H. Cilostazol prevents amyloid β peptide(25-35)-induced memory impairment and oxidative stress in mice. *Br J Pharmacol*. 2010;161:1899–1912.
124. Park SH, Kim JH, Bae SS, et al. Protective effect of the phosphodiesterase III inhibitor cilostazol on amyloid β-induced cognitive deficits associated with decreased amyloid β accumulation. *Biochem Biophys Res Commun*. 2011;408:602–608.
125. Senda J, Ito K, Kotake T, et al. Cilostazol use is associated with FIM cognitive improvement during convalescent rehabilitation in patients with ischemic stroke: a retrospective study. *Nagoya J Med Sci*. 2019;81:359–373.
126. Rishi MT, Selvaraju V, Thirunavukkarasu M, et al. Deletion of prolyl hydroxylase domain proteins (PHD1, PHD3) stabilizes hypoxia inducible factor-1 alpha, promotes neovascularization, and improves perfusion in a murine model of hind-limb ischemia. *Microvasc Res*. 2015;97:181–188.
127. Lijkwan MA, Hellingman AA, Bos EJ, et al. Short hairpin RNA gene silencing of prolyl hydroxylase-2 with a minicircle vector improves neovascularization of hindlimb ischemia. *Hum Gene Ther*. 2014;25:41–49.
128. Olson E, Demopoulos L, Haws TF, et al. Short-term treatment with a novel HIF-prolyl hydroxylase inhibitor (GSK1278863) failed to improve measures of performance in subjects with claudication-limited peripheral artery disease. *Vasc Med*. 2014;19:473–482.
129. Creager MA, Olin JW, Belch JJ, et al. Effect of hypoxia-inducible factor-1alpha gene therapy on walking performance in patients with intermittent claudication. *Circulation*. 2011;124:1765–1773.
130. Forster R, Liew A, Bhattacharya V, Shaw J, Stansby G. Gene therapy for peripheral arterial disease. *Cochrane Database Syst Rev*. 2018;10, Cd012058.
131. Haines DD, Tosaki A. Role of heme oxygenases in cardiovascular syndromes and co-morbidities. *Curr Pharm Des*. 2018;24:2322–2325.
132. Pei X, Kim H, Lee M, et al. Local delivery of cardiac stem cells overexpressing HIF-1α promotes angiogenesis and muscular tissue repair in a hind limb ischemia model. *J Control Release*. 2020;322:610–621.
133. Park JS, Bae SH, Jung S, Lee M, Choi D. Enrichment of vascular endothelial growth factor secreting mesenchymal stromal cells enhances therapeutic angiogenesis in a mouse model of hind limb ischemia. *Cytotherapy*. 2019;21:433–443.
134. Vulakh GM, Hingorani AP, Ascher E, Marks N. Adjunctive topical oxygen therapy for wound healing in patients with peripheral arterial disease. *Vascular*. 2022;17085381221080270.
135. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. *N Engl J Med*. 1996;334:1642–1648.
136. Leach R, Rees P, Wilmshurst P. Hyperbaric oxygen therapy. *Bmj*. 1998;317:1140–1143.
137. Kudchodkar BJ, Wilson J, Lacko A, Dory L. Hyperbaric oxygen reduces the progression and accelerates the regression of atherosclerosis in rabbits. *Arterioscler Thromb Vasc Biol*. 2000;20:1637–1643.
138. Asano T, Kaneko E, Shinozaki S, et al. Hyperbaric oxygen induces basic fibroblast growth factor and hepatocyte growth factor expression, and enhances blood perfusion and muscle regeneration in mouse ischemic hind limbs. *Circ J*. 2007;71:405–411.
139. Lin PY, Sung PH, Chung SY, et al. Hyperbaric oxygen therapy enhanced circulating levels of endothelial progenitor cells and angiogenesis biomarkers, blood flow, in ischemic areas in patients with peripheral arterial occlusive disease. *J Clin Med*. 2018;7.
140. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. 2019;58. S1-S109.e133.
141. Peng Z, Ren P, Kang Z, et al. Up-regulated HIF-1alpha is involved in the hypoxic tolerance induced by hyperbaric oxygen preconditioning. *Brain Res*. 2008;1212:71–78.
142. Burtscher J, Mallet RT, Pialoux V, Millet GP, Burtscher M. Adaptive responses to hypoxia and/or hyperoxia in humans. *Antioxid Redox Signal*. 2022;37:887–912.
143. Utrera A, Navarrete Á, González-Candia A, García-Herrera C, Herrera EA. Biomechanical and structural responses of the aorta to intermittent hypobaric hypoxia in a rat model. *Sci Rep*. 2022;12:3790.
144. Mallet RT, Manukhina EB, Ruelas SS, Caffrey JL, Downey HF. Cardioprotection by intermittent hypoxia conditioning: evidence, mechanisms, and therapeutic potential. *Am J Physiol Heart Circ Physiol*. 2018;315:H216–H232.
145. Mallet RT, Burtscher J, Richalet JP, Millet GP, Burtscher M. Impact of high altitude on cardiovascular health: current perspectives. *Vasc Health Risk Manag*. 2021;17:317–335.
146. Mallet RT, Burtscher J, Manukhina EB, et al. Hypoxic–hyperoxic conditioning and dementia. In: *Diagnosis and Management in Dementia*. Elsevier; 2020:745–760.
147. Shahid A, Stenson TH, Mcmurtry MS. Normoxic low-altitude simulation (at 714 mmHg) improves limb blood perfusion in mice with hindlimb ischemia. *Phys Rep*. 2021;9, e14228.