Atherothrombosis in Progression of Non-Coronary Artery Disease

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Peripheral artery disease (PAD) encompasses a variety of non-coronary artery diseases, and its prevalence varies based on screening approaches and clinical features. Recent data reveal a global prevalence of 80 million strokes, the majority (87%) of which are ischemic.

peripheral artery disease carotid stenosis

1. Introduction

Atherothrombosis represents the common pathophysiologic process in coronary and non-coronary artery disease in patients affected by atherosclerotic damage. Peripheral artery disease (PAD) involves the same cardiovascular (CV) risk factors as coronary artery disease (CAD), including arterial hypertension, diabetes mellitus, dyslipidemia, smoking, history of CV disease, chronic kidney disease, life habits, history of radiation therapy, psycho-social and genetic factors [1][2]. These shared factors explain the common finding of polyvascular artery disease, defined by the concomitant presence of relevant atherosclerotic disease in at least two vascular beds [1][2]. However, at variance with CAD and IS, smoking is the risk factor most strongly associated with lower extremity peripheral artery disease (LEPAD) [3]. Finally, differences in atherothrombosis pathophysiology have to be considered among carotid artery disease, abdominal aortic disease and LEPAD.

2. Carotid Artery Disease

Extracranial carotid atherosclerosis can be readily detected with non-invasive assessment such as high-resolution B-mode carotid ultrasonography (Duplex US), CT and MRI scan also able to detect subclinical atherosclerosis [1][2]. Carotid atherosclerosis leads to 25% of IS associated with disability and impaired prognosis [4]. Stenosis degree is one of the most important risk factors of ipsilateral IS, along with hemodynamic factors. Although hypoperfusion plays a role in the pathogenesis of IS, the majority of stroke events are attributed to embolization from unstable atherosclerotic plaque or carotid artery acute occlusion with thrombus distally detected [4]. As in coronary arteries, vulnerable plaque characteristics include a lipid-rich necrotic core with a thin/ruptured fibrous cap, ulceration and intraplaque hemorrhage (IPH) associated with the presence of inflammatory cells [4]. Carotid stenosis progression is also recently considered a marker of vulnerability, contributing to distal embolization and subsequent TIA [4]. IPH

represents one of the plaque progression factors with increased rupture risk and future risk events [4]. Further pathophysiologic findings on vulnerable plaque highlight the role of inflammation in atherosclerosis with intraplaque angiogenesis and hypoxia in cerebral adverse events. Hybrid imaging, such as PET/CT or PET/MRI, can detect plaque rupture features [4]. Some morphologic characteristics, such as ulceration and IPH, are also associated with the occurrence of ischemic events, independently of the degree of stenosis. Recent data from the American Society of Neuroradiology showed that the annualized event rates of ipsilateral stroke in those with IPH are higher than in patients without IPH irrespective of stenosis degree: 9.0% versus 0.7% (<50% stenosis), 18.1% versus 2.1% (50–69% stenosis) and 29.3% versus 1.5% (70–99% stenosis), confirming IPH as an independent predictor of ipsilateral stroke (Hazard Ratio—HR 3.3; 95% confidence interval—CI, 1.4–7.8) [4]. Plaque calcification represents a stabilizing factor in carotid artery disease with less inflammation, neovascularization and IPH and lower likelihood of rupture [4]. Furthermore, several atherosclerosis-related factors such as aging, inflammation and ischemia increase circulating levels and deposition of amyloid-beta (Aβ) in intracranial arteries contributing to different types of dementia with impaired cognitive performance. Moreover, among Aβ peptides, Aβ1-40 was independently associated with impaired vasodilating properties, higher IMT, low ABI, as well as coronary and aorta arterial damage, with a worse prognosis in elderly patients [5]. These findings highlight the interplay between dementia and CVD, particularly driven by diffuse atherosclerosis, although current Aβ pathophysiology and therapeutic options are still uncertain areas.

3. Abdominal Aortic Disease

Atherosclerosis is frequently associated with abdominal aortic disease, especially in polyvascular disease [6][7]. While the pathophysiologic role of atherosclerosis in medium and small arteries is well-known, the relationship with abdominal aortic disease is incompletely understood. Acute abdominal aortic thrombosis is a fatal and rare condition, and abdominal aortic disease is mostly represented by AAA, which arises as a pathological response to aortic atherosclerosis [7]. In animal models, inflammatory pathways, along with aortic matrix degradation and hemodynamic forces, lead to AAA development [7]. During intraluminal stenosis development, the atherosclerotic process includes compensatory chronic inflammatory changes in the media with extracellular matrix remodeling promoting artery diameter growth leading to the development of an aortic aneurysm [7]. Moreover, aortic media chronic inflammation driven by myo-fibroblast favors aortic false lumen development with chronic aortic dissection origin [6]. To date, the interplay of chronic dissection and aneurysm is not completely understood. Chronic aortic dissection leads to more rapid aortic aneurysm growth than non-dissected aorta [6]. Arterial pressure and relative wall tension drive false lumen propagation in the aortic axis with a high rupture risk, which overcomes the remodeling capability of aneurysmatic artery wall [6]. In addition, partial chronic abdominal aortic thrombosis is a common finding in patients with chronic aortic dissection and/or aneurysm [8]. Often, aortic thrombus shows a multi-layered morphology with dense fibrin and inflammatory cells such as leukocytes and platelet-derived proteins with proteolytic proprieties and increased risk of peripheral embolism [8]. Around 40% of chronic aortic dissection patients require urgent revascularization for aortic rupture and/or branch vessel hypoperfusion [6]. New understandings are evolving from combining 3- and 4-dimensional CT morphology data, MRI flow data, computer simulation of fluid dynamics and the fields of biomechanics and mechanobiology, which may help to better

comprehend the physiopathologic key elements leading to false lumen degeneration and aneurysm development and facilitate the development of novel treatments and appropriate timing for them in patients affected by chronic aortic dissection and aneurysm [9][10].

4. Lower Extremity Peripheral Artery Disease

Atherosclerosis is a common LEPAD feature that can explain symptoms and signs related to different clinical presentations, from claudication to ALI/CLTI [11]. Lower extremity peripheral arteries represent a very diverse arterial bed with several differences and related clinical scenarios between itself. One difference is driven by anatomical factors (e.g., arterial diameter) considering large vessels (e.g., iliac–femoral axis, popliteal artery) and smaller vessels below the knee (BTK) [12]. Consequently, flow characteristics and atherosclerotic complications will be different. Overall, compared to cerebrovascular disease and CAD, the role of atherothrombosis in the progression and complications of LEPAD is less clear and studied. Atherosclerosis causes claudication, which represents the clinical manifestation of significant atherosclerotic stenosis during exercise and relief within 10 min rest. Particularly, symptoms stem from the muscles perfused by the stenosed artery [2][6]. Similar to chronic CAD, claudication represents the chronic manifestation of LEPAD, with management depending mostly on CV risk factor and physical exercise management [2][6]. Considering atherothrombotic complications of LEPAD, approximately 10% of patients with claudication develop chronic limb-threatening ischemia (CLTI) within 5 years, contributing to poor prognosis, including 1-year rates of mortality of 25% and 1-year rates of amputation of 30% [11]. The main difference from CAD atherothrombosis is the occurrence of thrombotic events even in the absence of significant atherosclerotic disease. Histopathological analysis on LEPAD presenting with CLTI shows that thrombotic occlusion in the BTK district is the main cause of disease even in patients without significant atherosclerosis, while significant atherosclerotic lesions were more often detected in the femoral-popliteal artery [12]. On the contrary, ALI and related thrombus often occur in patients with both significant and non-significant atherosclerosis, while small vessel obliteration is driven by media calcification, intimal fibrosis and superimposed cholesterol emboli [12]. Similar to acute MI, ALI is characterized by a sudden decrease in limb perfusion that often results in tissue loss and requires early intervention. However, in contrast to atherothrombotic acute coronary events, ALI in patients with PAD is driven not only by atherothrombosis but also by emboli from the heart and proximal vessels and graft occlusion in patients with previous lower extremity revascularization (LER) [13]. Several pieces of evidence support the thromboembolic origin of CLTI/ALI-affected popliteal and BTK artery rather than stenotic atherosclerotic disease. The embolic source is often an aorto-iliac-femoral atherosclerotic plaque with subsequent lumen obliteration of a distal smaller artery [12]. The main differences between ALI and CTLI are represented by the duration of symptoms (less vs. more than two weeks), clinical presentation (acute vs. chronic), presence of collateral arteries in CTLI and timing of revascularization (urgent in order to address the high risk of amputation vs. non-urgent in order to minimize tissue loss) [14].

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