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Peripheral Arterial Disease

A Practical Approach

Edited by Nishtha Sareen and Abhishek Ojha

PERIPHERAL ARTERIAL DISEASE - A PRACTICAL APPROACH

Edited by **Nishtha Sareen**
and **Abhishek Ojha**

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http://dx.doi.org/10.5772/intechopen.72407
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First published in London, United Kingdom, 2018 by IntechOpen
eBook (PDF) Published by IntechOpen, 2019
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, The Shard, 25th floor, 32 London Bridge Street
London, SE19SG – United Kingdom
Printed in Croatia

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Additional hard and PDF copies can be obtained from orders@intechopen.com

Peripheral Arterial Disease - A Practical Approach
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p. cm.

Print ISBN 978-1-78984-217-3

Online ISBN 978-1-78984-218-0

eBook (PDF) ISBN 978-1-83881-684-1

Meet the editors

Dr Nishtha Sareen is a female Interventional Cardiologist board certified in Echocardiography, Nuclear Medicine, Interventional Cardiology and Endovascular Interventions. After completing her medical school in India with gold medals in 10 out of 13 medical subjects and first position in the University of Rajasthan comprising of 13 medical colleges, Dr Sareen completed her sub-internship with "High Honors" at Harvard Medical School, Boston. Following this, she completed her training in Internal Medicine at LIJ Medical Center in New York and Cardiology at St Joseph Mercy Oakland, Michigan. She trained in Interventional Cardiology at the coveted Mount Sinai Medical Center, New York. With more than 118 publications and presentations, and numerous National and International awards, Dr Sareen is dedicated to enthusiastic academic teaching of medical students, residents, fellows and fellow physicians as part of many frontline associations in the US. Dr Sareen is passionate about Women Heart Health and nurtures the revolution "Women-hood without Stents".

Dr Abhishek Ojha is a graduate of Rabindra Nath Tagore Medical College in India. With a glorious academic career that includes the highest division in medical college subjects, academic position in the top 0.1% of students in the country and gold and silver medals, Dr Ojha has completed more than 100 publications and presentations. Dr Ojha completed his sub-internship at Harvard Medical School, Boston and Yale School of Medicine, New Haven. He has since been involved in active clinical research, which encompasses cardiac physiology, medical pharmacology, quality improvement projects in NSTE ACS patients and projects to study and improve the current educational infrastructure in cardiology fellowships. Dr Ojha has extensively studied the epidemiological medical issues in various communities in varied age groups and their impact on dispensing quality care. Dr Ojha is passionate about teaching and contributing to the ever-fascinating field of Cardiology and Research.

Contents

Preface

"Peripheral Arterial Disease - A Practical Approach" is an attempt to summarize and discuss the most pertinent practical aspects of peripheral vascular disease, its clinical implications, diagnostic testing, therapeutic interventions and innovations. This book is an honest effort to provide a clinically relevant approach to the management plan in patients presenting with peripheral vascular symptoms. We intend to provide our readers with additional ground-breaking strategies, which may evolve as vital interventions as this ever-fascinating field continues to progress. We have incorporated an Introductory chapter on the diagnostic modalities in peripheral atherosclerotic disease and additional chapters ranging from superficial femoral stenosis, approach to superficial femoral and popliteal chronic total occlusions, risk factors in carotid stenosis, cardiovascular risk evaluation in leg ischemia to the evolving field of genetics in peripheral arterial disease. By providing this diverse array of topics to our readers, we hope this book serves as a clinical guide for cardiology fellows and practicing interventional cardiologists.

I would like to thank the authors for their time and effort in bringing about the character of this publication. I extend sincere gratitude to my co-editor Dr. Abhishek Ojha for his relentless work in reviewing the chapters. I would also like to thank the publishers for bringing about this book in its current form.

I hope you enjoy reading this book as much as we enjoyed working on it.

Warmly,

Nishtha Sareen and Abhishek Ojha
Michigan State University, USA

Superficial Femoral Artery and Popliteal Artery

Chapter 1

Introductory Chapter: Superficial Femoral Arterial Disease

Yashwant Agrawal, Abhishek Ojha and
Nishtha Sareen

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.81097

1. Introduction

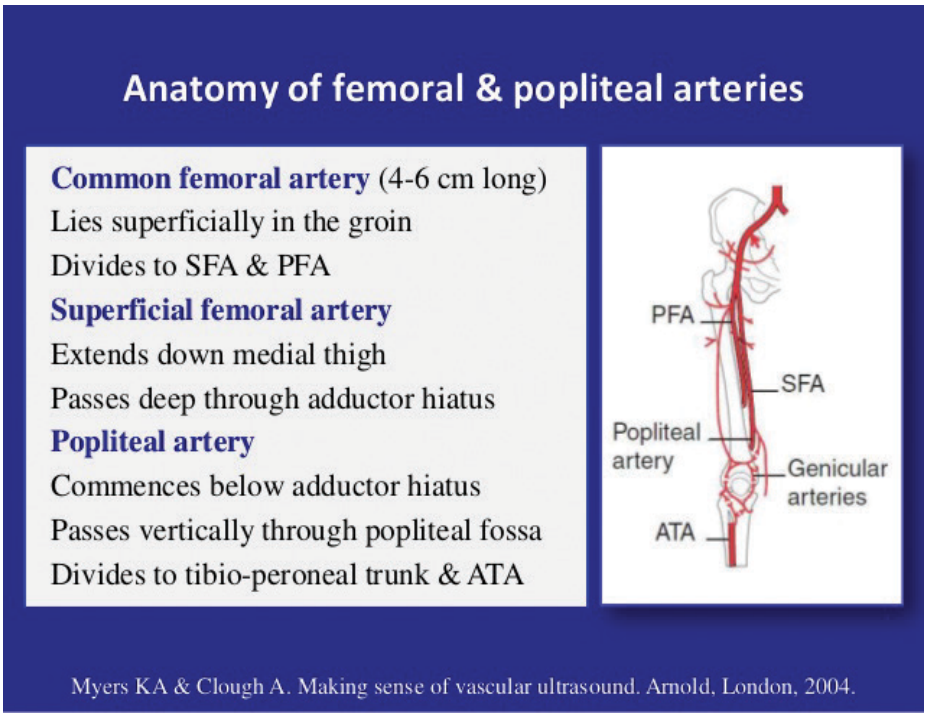
Superficial femoral artery, traditionally grouped together with the popliteal artery, as femoral popliteal segment, is the most common localization of peripheral artery disease (70%). Atherosclerotic disease of superficial femoral artery is deemed high risk to present with diffuse distribution, frequent calcification, large plaque burden, and high progression rate to total occlusion [1]. Additionally, femoral popliteal segment is exposed to significant flexion, bending, and compression forces. Hence, unique anatomical features, along with nonfavorable atherosclerotic plaques characterize in this region, contributes to a significant challenge, when treating this disease. Apart from the variation in the anatomy and the presentation of the pathology in superficial femoral artery area, there are many unique features in the presentation and diagnosis as well. These in concert with the downstream areas of supply at risk, can present with pain on exertion, pain at rest, or/and with nonhealing ulcers extending anywhere from thigh to feet area. It is crucial to understand that while these issues could arise from focal stenosis at the presentation level, consideration should always be given to an inflow lesion.

2. Anatomy

Superficial femoral artery arises, at the level of the femoral head, as the continuation of the common femoral artery, medially and anteriorly to profunda femoral artery. After the origin, superficial femoral artery enters the femoral triangle, coursing toward the abductor canal. Subsequently, it leaves the abductor canal through abductor hiatus to enter the popliteal fossa.

At this level, the artery name is changing to the popliteal artery, which usually bifurcates into the anterior tibial artery and tibioperoneal trunk. One of the unique features of superficial femoral artery is lack of the major branches. The only named branch is the descending genicular branch, contributing to collateral flow of the knee when there is a stenosis in the area. Additionally, when discussing the superficial femoral artery disease, profunda femoral branch deserves a special attention, as the potential source of significant collateral flow, which should be evaluated before decision-making about the intervention on superficial femoral artery [2].

Anatomy is especially important when evaluating the superficial femoral arterial stenosis in patients with concerning clinical presentation on abdominal aiortogram with run-off. In cardiac catheterization laboratory, we place a pigtail in the abdominal aorta above the level of iliac bifurcation. There is an option of performing stepped digital subtraction views with 100 ml contrast at the rate of 10–15 ml/sec. The alternative option is to cross over the iliac artery of the affected lower extremity and then use 50 ml contrast at the flow rate of 10 ml/sec for the imaging. Adequate images can be obtained if patient does not move the lower extremities.



3. Pathophysiology of superficial femoral arterial (SFA) disease

While the pathology can range from atherosclerosis to thrombosis, the majority is attributed to atherosclerosis in the lower extremities. The detailed pathophysiology has been described in the chapter of aortoiliac disease. As outlined above, atherosclerotic disease of superficial femoral

artery is characterized by diffuse distribution, significant plaque burden, frequent calcification, and the high risk of progression to total occlusion, which is likely dictated by distinguishable anatomical features, including significant length of the segment, measuring about 50 cm in an average adult patient. The management is dictated by the extent, location, and intensity of the stenosis and calcification. It can range from medical therapy alone to aggressive interventional approaches. The interventional approaches can range from percutaneous interventions to surgical interventions, again based upon the extent of pathology and patient clinical risk factors.

4. Clinical symptoms and diagnosis

Clinically, intermittent claudication is the classic symptom of peripheral arterial disease (PAD). Usually, patients with SFA disease endorse pain in the upper two-thirds of the calf. Nevertheless, approximately only 10% of patients report these symptoms. About half of them complain about atypical leg pain and about 40% remain asymptomatic. Acute limb ischemia is an uncommon presentation (1–2%) [3]. However, it can be limb threatening.

Usually, the diagnosis of PAD is made clinically based upon symptoms and signs. Physical examination typically reveals diminished peripheral pulses and skin changes over the poorly supplied area. Elevation pallor and dependent rubor are signs of advanced PAD. Physical examination may be helpful in localizing the segment of obstruction. Intact femoral pulses, diminishing peripherally and vascular bruit over the SFA are suggestive about this vessel involvement. Ankle brachial index (ABI) is a useful confirmatory test for PAD (ABI ratio < 0.9). Pursuing topography is justified in case of potential intervention. The approach to the patient with suspected PAD and information about testing modalities were outlined in detail in the chapter dedicated to aortoiliac disease.

5. Classification

Clinical symptoms are the fundaments of Fontaine classification. This is a widely used system, encompassing four stages of PAD, ranging from asymptomatic disease to apparent necrosis of the limb (**Table 1**). Similarly, Rutherford classification included patient's symptoms, but was enriched by objective data, not requiring invasive measures (**Table 2**) [4].

Anatomically, SFA has been grouped together with neighboring arterial vessels as the femoral popliteal segment. This facilitates the management even more significantly. Further anatomical details about the lesion, including the disease pattern and the number of changes, were incorporated into Trans-Atlantic Inter-Society Consensus (TASC II). This classification distinguishes type A, B, C, and D type. Accordingly, lesions vary from relatively short stenosis or occlusion to more diffuse changes. This dictates the management plan from medical therapy to revascularization. Importantly, TASC II additionally provides guidelines regarding the treatment strategy, based on intervention success rate. Detailed classification, in relation to femoral popliteal segment was presented in **Table 3** [5].

Stage I – No symptoms
Stage II – Mild claudication
Stage IIa – Intermittent claudication >200 m walking distance
Stage IIb – Intermittent claudication <200 m walking distance
Stage III – Pain at rest
Stage IV – Ulceration/gangrene due to ischemia

Table 1. PAD classification system by Fontaine.

Grade	Category	Presentation	Objective measures
0	0	No symptoms	Treadmill test and reactive hyperemia test within normal limits
	1	Mild intermittent claudication	Can complete treadmill test. Ankle pressure post exertion >50 mmHg, but ≥20 mmHg lower than at rest
I	2	Moderate intermittent claudication	Between mild and severe claudication
	3	Severe claudication	Unable to complete treadmill test. Ankle pressure post exertion <50 mmHg
II	4	Symptoms at rest	Ankle pressure <40 mmHg at rest. Toe pressure <30 mmHg
III	5	Minor tissue loss, focal gangrene, and ischemic ulceration	Ankle pressure <60 mmHg at rest. Toe pressure <40 mmHg
	6	Tissue loss spreading above metatarsal level, extremity cannot be preserved any longer	Same as above

Table 2. PAD classification system by Rutherford.

Type A lesion
Solitary stenosis <10 cm in length
Solitary occlusion <5 cm in length
Type B lesion
Solitary, severally calcified stenosis <5 cm in length
Many lesions, each <5 cm in length
Solitary lesion <15 cm in length
Type C lesion
Multiple lesions totaling >15 cm in length
Recurring lesions after treatment failure
Type D lesion
Chronic total occlusion of SFA > 20 cm in length.

Table 3. SFA lesions – TASC II classification system.

6. Treatment

All patients with PAD should be treated initially the same way with pharmacotherapy, including antiplatelet medications and high-intensity statin, risk factors control, and exercise program, irrespectively of the localization of the lesion. Medical therapy is paramount in the management and should be instituted. Revascularization is a modality reserved for selected cases, including no adequate symptoms control despite appropriate conservative treatment and acute limb ischemia [6]. Detailed information regarding conservative management based on the most recent trials was outlined in the chapter of aortoiliac disease.

7. Revascularization

Revascularization, as mentioned above, is a treatment option only for selected patients with SFA disease. Traditionally, femoral popliteal segment used to be treated with vein bypass surgery. Nevertheless, over the last decades, a rapid evolution of endovascular techniques revolutionized the treatment of PAD. Admittedly, endovascular treatment of SFA disease appears to be specifically complex due to unique biophysical forces over his body area along with often diffuse and calcified atherosclerotic lesions, leading to suboptimal endovascular treatment results and stent restenosis as the significant problem affecting long-term outcome. However, the tendency is pointing toward improving morbidity and mortality index after endovascular treatment [7]. Currently, according to TASC II Update (2015), endovascular approach is the preferred method of treating femoropopliteal lesion up to 10 cm in length [5]. Different modalities of invasive treatment have been presented in a separate chapter.

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Chapter 2

Interventional Strategies for the Superficial Femoral Artery

Rudin Gjeka

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.76724

Abstract

The incidence of peripheral arterial disease (PAD) is rising due to significant increase in metabolic disease such as diabetes mellitus, increase in aging population, and tobacco use. Superficial femoral artery (SFA) disease is the leading cause of peripheral artery disease and claudication. In the last decades, several technologies/techniques have been developed for the treatment of SFA atherosclerotic disease including balloon angioplasty, balloon expanding stents, self-expanding stents, drug-eluting balloon, and atherectomy. The advances made in technology have significantly improved the quality of the balloons, but they have limitations especially in long and calcified lesions. While the initial studies using stainless steel stents failed to show any significant difference in outcomes, understanding the pathophysiology and improvement in stent technologies has shown significant reduction of restenosis by five- to sevenfold when compared to angioplasty alone. Atherectomy is another modality of plaque modification and treatment, which can be done as a stand-alone treatment or more commonly combined with PTA and/or stenting. Finally, several randomized studies and registries have showed that with improvement in technology, there is significant improvement in long-term outcomes of SFA atherosclerotic disease.

Keywords: superficial femoral artery angioplasty, superficial femoral artery stenting, SFA rotational atherectomy, SFA laser atherectomy, SFA directional atherectomy

1. Introduction

The incidence of peripheral arterial disease (PAD) is rising due to significant increase in metabolic diseases such as diabetes mellitus, increase in aging population and tobacco use.

PAD is the third cardiovascular cause of morbidity following the coronary artery disease and stroke.

Superficial femoral artery (SFA) disease is the leading cause of peripheral artery disease and claudication. According to current estimates, there are over 8 million people affected with PAD and the numbers are rising. Nearly half of the patients affected from PAD are asymptomatic and about 20% have claudication [1–4]. Regardless if the patients are symptomatic or not, patients with PAD have worse quality of life and worse outcomes when compared to people that do not [5].

Nearly 50 years after the first endovascular intervention of the SFA performed by Charles Dotter, endovascular intervention of the lower extremity has increased significantly [6]. The relatively low risk for morbidity and mortality and improvement in technology have seen a high success rate making the endovascular intervention of the SFA the preferred choice, particularly in short-segment disease [7]. Nevertheless, the unique biochemical, anatomical, and hemodynamic forces the SFA is exposed to, makes the endovascular intervention quite challenging.

Rutherford category	Characteristic
0	Asymptomatic
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Pain at rest
5	Minor tissue loss
6	Major tissue loss

Table 1. Rutherford classification of chronic limb ischemia.

Trans-Atlantic Inter-Society Consensus II classification of femoropopliteal disease		
Type lesion	**Stenosis or occlusion pattern**	**Procedure**
A	Single stenosis less or equal to 10 cm or occlusion less or equal to 5 cm.	Endovascular
B	Multiple stenosis or occlusion less or equal to 5 cm or a single severely calcified occlusion of 5 cm or less. Single stenosis or occlusion of 15 cm or less, not involving below the knee popliteal artery. Single or multiple lesions in conjunction with occluded proximal infra-geniculate vessels to improve inflow for distal bypass. Single popliteal artery stenosis.	Endovascular
C	Multiple stenosis or occlusion adding to more than 15 cm irrespective of calcification. Two failed attempts for endovascular revascularization.	Endovascular or Surgical bypass
D	Chronic occlusions of the CFA, more than 20 cm of SFA stenosis, popliteal artery or proximal trifurcation vessels.	Surgical bypass

CFA = Common Femoral Artery. SFA = Superficial Femoral Artery.

Table 2. Trans-Atlantic inter-society consensus II (TASC II). Classification of the femoropopliteal disease.

Indications to intervene upon the lower extremities depend on the severity of disease and symptoms with absolute indications in cases with limb-threatening ischemia with resting pain and tissue loss (including Rutherford classification class 4–6). Relative indications are not limb threatening but significantly debilitating and often a reason to intervene upon and include mainly patients with intermittent claudication (Rutherford class 2 and 3), [8] (**Table 1**).

Once intervention is indicated, the decision to intervene via endovascular approach rather than open surgical approach is mainly based upon the Trans-Atlantic inter-Society Consensus II Classification (TASCII) recommendations [7] (**Table 2**).

2. Vascular access technique

Like all endovascular interventions, SFA interventions begin with vascular access. The most common vascular access is the common femoral artery (CFR). In selected cases, brachial artery can be used as well. For safety purposes and in attempting to reduce complications, the recommended technique is the ultrasound (US)-guided technique and if possible micropuncture needle can be used as well.

Using the ultrasound permits direct visualization of the artery and its branches. US-guided access reduces multiple punctures and as such reduces the incidence of arteriovenous fistulas. US-guided technique is an excellent choice in patients with no palpable pulse, heavily diseased common femoral artery (CFR), obese patients, and high bifurcation [9].

Puncture using anatomical landmarks is another approach several operators use. The point of maximal pulsation correlates with the midpoint of the CFA in over 92% of the cases. When the pulse is difficult to palpate, the midpoint between the anterior superior iliac spine and pubic tubercle by palpation is used. The groin crease is an unreliable marker and is located distal to the CFA bifurcation and is located distal to the CFA bifurcation in about three out of four patients. Fluoroscopy-guided puncture can be used as well, aiming the inner lower third of the femoral head. The femoral head provides a solid surface for firm compression of the CFA necessary for hemostasis following arterial puncture [10–12].

Arterial access can be obtained on either side with the contralateral side being the preferred in most cases. The contralateral access remains the preferred choice as it allows an adequate working length to image and treat the sequential lesions within the entire target extremity. Once the access is obtained, a guide wire is introduced with size 0.018–0.035-in depending on if it is a micropuncture or not. Sheath sizes used for the SFA intervention range from 4 to 7 French. Sheaths protect the access vessel during the catheter intervention and wire exchanges during a procedure. The smallest size sheath to complete the intervention should be used. A reverse curved catheter and a 0.035-in guide wire are usually used to crossover the aortic bifurcation. The guide wire is then advanced to the level of the CFA and at that point allows to advance a catheter to the distal external iliac artery. At this point, serial lower extremity angiograms can be performed at the target extremity. Patency of the runoff vessels is very important to assess prior to intervention. Clinically assessing the presence of pulses is very important because distal vessels can be occluded secondary to embolization from the SFA

intervention. In presence of single-vessel runoff, an embolic protection filter can be used prior to intervention to minimize distal embolic occlusion. Prior to starting intervention, the patient should be heparinized with an activated clotting time (ACT) of 250 seconds or more [13].

After the patient is anticoagulated, the target SFA lesion must be crossed. This is achieved using a directional catheter and a 0.035-in wire, usually a hydrophilic wire. The catheter is usually positioned just proximal to the target lesion providing wire support and pushability to cross the stenosis. Remaining intraluminal is the preferred technique to cross the lesion, but it is not possible with a 0.035-in wire. Therefore, an attempt can be made by using a 0.018-inch or a 0.014-inch guide wire and catheter. If there are still difficulties in crossing the lesion, then a subintimal approach can be attempted. When the reentry with a hydrophilic wire is not possible, then the use of a reentry device is recommended. Subintimal angioplasty can be performed effectively with excellent technical success and acceptable patency [14–16].

3. Balloon angioplasty

Balloon angioplasty remains the most frequently used technique in the treatment of SFA disease as either primary or adjunctive therapy for stents and other devices. After crossing the lesion, an appropriate balloon must be selected. There are several balloons that can be used in different scenarios as we describe later [20].

The noncompliant balloons inflate to a uniform diameter regardless of the amount of pressure introduced in the balloon. As such, the noncompliant balloons are often preferred because they are less likely to cause injury to the native vessel and are more effective in treating atherosclerotic lesions. Balloon catheters can be over the wire, and they offer more pushability and often times are better in crossing tight lesions. Furthermore, these balloons can be used as catheters as well. Monorail or the rapid exchange balloons are less cumbersome and easier to handle as they use shorter wires. However, these advantages come at the expense of the pushability, and crossing a tight lesion with a monorail balloon can be more challenging. The diameter of a normal SFA segment distal to the lesion is used as a reference to size the angioplasty. To size the length of the balloon, a radiopaque external ruler is used. The proper length of the balloon must treat the target lesion without disruption of the normal segment proximal and distal to the lesion [17].

The nominal pressure of a balloon is the pressure at which the balloon will achieve the manufacturer's stated diameter. With noncompliant balloon, increasing the pressure will not result in increase in diameter, while with compliant or semi-compliant balloons, an increase in pressure will result in balloon overinflation to a larger diameter. Overinflation and over-sizing the balloon can cause trauma to the artery or significant dissection. The burst pressure is the pressure at which 99.9% of the balloon will not rupture. This pressure should not be exceeded. Balloon can rupture due to overinflation or if the atherosclerotic plaque is heavily calcified. Balloon rupture can cause embolization of balloon fragments or air embolization if the balloon is not properly prepped [17, 18].

When planning on performing only angioplasty without stent placement, longer balloon inflation times are used to stabilize the luminal surface of the arterial segment being treated. The longer inflation times may reduce a flow-limiting dissection. After the intervention, angiography is performed; if there is any vessel recoil, persistent stenosis, or a flow-limiting dissection, repeat angioplasty is recommended. In these circumstances, increase of inflation times is recommended [17, 19].

Conventional balloons are associated with a high rate of uncontrolled dissections that may require bailout stenting, particularly in more complex and diffuse SFA lesions. Cutting balloons are reinforced with microtomes that provide a leading edge to cut through stiff fibrotic lesions at lower pressures. These types of balloons are suggested instead of using larger diameter balloons and may be associated with less hemodynamically significant dissections. Studies have shown that use of cutting balloons have shown better long-term patency in peripheral artery interventions. When there is a persistent residual stenosis of more than 50% or a flow-limiting dissection after the PTA, provisional stenting is performed [20].

With improvement in technology, development of newer balloons, such as drug-coated balloons (DCB), have significantly improved outcomes in percutaneous interventions of the peripheral arteries including the SFA disease. Tepe G et al. conducted a randomized controlled study of 331 patients with symptomatic femoropopliteal artery disease up to 18 cm in length. At 24 months, outcomes from the trial revealed a durable and superior treatment effect of the DCB versus percutaneous transluminal angioplasty (PTA) with significantly higher primary patency, lower clinically driven target lesion revascularization (TLR), and similar functional status improvement with fewer repeat interventions [21].

Drug-coated balloons have been also studied in complex stenosis such as in-stent restenosis (ISR). Brodmann et al. performed a study to assess the effectiveness and safety of the use of paclitaxel-coated drug-coated balloon (DCB) in patients with de novo in-stent restenosis (ISR). A total of 131 patients were enrolled. Procedural success was achieved in 98.5% of subjects. Primary patency estimate was 88.7% in the ISR cohort at 12 months. Freedom from clinically driven target lesion revascularization (CD-TLR) estimated at 92.9% at 12 months [22].

4. Stenting

The efficacy of stenting over the balloon angioplasty failed to show any significant advantage in the early randomized trials where mainly stainless steel bare-metal stents were used [7, 23, 24]. However, with the advancement in stent technology, further newer studies compared primary angioplasty to Nitinol stents in the SFA. Interestingly, these studies revealed that angioplasty alone results in equivalent patency rates when compared to primary stenting in patients with short lesions. On the other hand, longer stenosis are best treated with primary stenting and that offers longer time patency (**Table 3**).

The FAST trial, a multicenter randomized controlled trial, compared the SFA PTA and nitinol stenting in 244 patients. The indication to treat was claudication in 97% of patients in both groups. The mean lesion length was relatively short, 4.4 cm in the stenting group and 4.5 cm in

Trial	Device	Sample size	Average lesion length (mm)	Primary end point	Stent patency rate %
Bare metal stents					
Resiliant Laird et al. [27]	LifeStent versus PTA	206	71 ± 44 BMS 64 ± 41 PTA	TLR at I year	81/37, 1 year (p = 0.0001)
FAST Krachenberk et al. [25]	Bard Luminexx vs. PTA	244	53.4 ± 29.5 BMS 51.1 ± 24 PTA	Binary restenosis at 1 year	68/62, 1 year (p = 0.377)
Absolute Schillinger et al. [26]	Dynalink/Absolute vs. PTA	104	132 ± 71 BMS 127 ± 55 PTA	Binary restenosis at 6 months	75/55, 6 months (p = 0.05) 63/37, 1 year (p = 0.01)
Drug-eluting stents					
SIROCCO I Duda et al. [34]	Sirolimus coated vs. SMART	36	82.9 DES 88.6 BMS	In-stent luminal stenosis at 6 months	100/77, 6 months (P = 0.10)
SIROCCO II Duda et al. [55]	Sirolimus coated vs. SMART	57	86.5 ± 37 DES 76.3 ± 46 BMS	In-stent luminal stenosis at 6 months	100/93, 6 months (p = 0.46)
SIROCCO Long term Duda et al. [56]	Sirolimus coated vs. SMART	93	85 ± 44 DES 81 ± 52 BMS	In-stent luminal stenosis at 6 months	77/79, 2 years (p > 0.05)
Zilver PTX Drake et al. [34]	Zilver PTX vs. PTA	479	66.4 ± 38.9 63.2 ± 40.5	Event free survival and patency	83/33, 1 year (p < 0.001) 75/27, 2 years (p < 0.01)

Table 3. Landmark trials for PAD and stenting.

the PTA group. Results revealed comparable amputation and mortality rates. No significant differences were noted in the restenosis rates (38.6% in the PTA group vs. 31.7% in the stent group) or change in clinical status between the two groups. The ankle-brachial index remained the same at 12 months [25].

The Vienna-ABSOLUTE study was the first randomized study to show superiority of primary stenting over balloon angioplasty for the treatment of moderate-length SFA lesions, 13.2 cm in the stenting group, and 12.7 in the PTA group. In this study, 104 patients were included, and patients were randomized 1:1 to a Dynalink or Absolute stent versus balloon angioplasty. The indication for treatment was claudication in the majority of cases, 88% in the stent group and 87% in the PTA group. The groups did not defer in limb salvage or mortality. The restenosis rate was greater in the PTA group (43 vs. 24%, p = 0.05). Duplex ultrasound at 12 months also demonstrated a greater restenosis rate in the PTA group (63 vs. 37%, p = 0.01). Furthermore, the maximal walking distance was significantly less in the PTA group at 6 and 12 months (267 vs. 387 m, p = 0.04) [26]. The groups did not defer in limb salvage or mortality. The restenosis rate was greater in the PTA group (43 vs. 24%, p = 0.05). Duplex ultrasound at 12 months also demonstrated a greater restenosis rate in the PTA group (63 vs. 37%, p = 0.01). Furthermore, the

maximal walking distance was significantly less in the PTA group at 6 and 12 months (267 vs. 387 m, $p = 0.04$).

Another study that showed significant superiority of stenting versus PTA is the RESILIANT trial. A multicenter randomized controlled trial (RCT) comparing the PTA to nitinol stenting in 206 patients [27]. Indication for treatment was claudication and the lesion length was in the moderate range (7.7 cm in the stent group and 6.4 cm in the PTA group). The 6-month primary patency was worse in the PTA group when compared with primary stenting (47.4 vs. 94.2%, $p = 0.0001$). Patients were followed up at 12 months and results remained statistically significant in the stenting group (36.7% in the PTA group vs. 81.3% in the stenting group, $p = 0.0001$). Even longer term, 3-year follow-up, patients randomized to primary stent placement had significantly higher freedom from target lesion revascularization (75.5 vs. 41.8%) [28]. The earlier-mentioned studies provided strong evidence favoring the primary stenting as the treatment choice for moderate-length SFA lesions.

Based on recent registry studies, current-generation nitinol self-expanding stents have improved primary patency, with low to zero rates of stent fractures [29, 30]. The SUMMIT study was a prospective multicenter registry study of the Epic stent, which is a laser-cut nitinol self-expanding stent [29]. At 1-year follow-up, the restenosis rate was 15.7%, with a freedom from the target lesion revascularization (TLR) rate of 92%. No stent fractures were noted on follow-up patients with available X-rays.

COMPLETE SE trial is a prospective multicenter, single-arm study that evaluated the self-expanding stent in SFA and proximal popliteal for de novo and/or restenotic lesions in patients with symptomatic PAD [30]. At 1-year follow-up, the primary patency rate was 72.6%, with a clinically driven.

5. Recent development in SFA stents

Technology continues to undergo significant improvement in SFA stents with the goal to increase durability and conformability with better long-term patency. The Supera stent (Abbott Vascular) is a recently approved stent with a novel woven design that results in improved radial strength, flexibility, and resistance to fracture. The SUPERB study reported a primary patency rate of 86% in the pivotal registry [31]. Other stent designs under investigation include the Tigris stent (Gore and Associates), which has a nitinol wire frame with Extended polytetrafluoroethylene (ePTFE) coating and interconnecting ePTFE-linking regions. The SMART Flex stent (Flexible Stent Solutions) has a helical strut bands and flex bridges that provide flexibility while maintaining longitudinal integrity. The BioMimics 3D stent (Veryan Medical) has a helical design that may promote laminar flow.

Considering the success of the drug-eluting stents over the bare-metal stents in the coronary arterial disease, similar stent technology was developed for the peripheral arterial disease hoping for similar results. Several early studies failed to demonstrate clinical superiority when

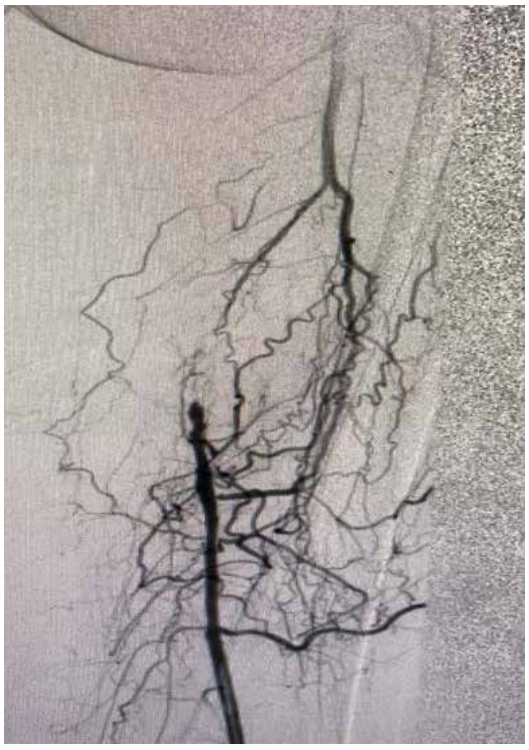

Figure 1. There is an example of retrograde approach of the SFA CTO (chronic total occlusion) intervention with PTA and two Zilver PTA self expanding drug eluting stents (pre intervention).

compared to bare-metal stents in the SFA. These early studies included both sirolimus-eluting and everolimus-eluting designs using an earlier-generation platform [32, 33].

With subsequent development of DES technology, paclitaxel-eluting stent has shown significant benefit in the SFA treatment when compared to both balloon angioplasty and placement of a bare-metal stent. The Zilver-PTX is a nitinol scaffold stent with a polymer-free coating that elutes paclitaxel [34]. In the ZILVER PTX study, patients were randomized to placement of a paclitaxel-eluting Zilver stent versus balloon angioplasty. A second arm of the study randomized patients to Zilver PTX versus bare-metal stenting in cases of failure of balloon angioplasty. At 1 year, the primary patency rate was 83% in the DES group versus 32% in the PTA group. In the second-arm randomization, 1-year primary patency with Zilver PTX was superior to the Zilver BMS (89.9% vs. 73%). These results showed significant superiority of the Zilver PTX to both angioplasty alone and the Zilver bare-metal stent (**Figures 1** and **2**).

Based in the above results, DES use in SFA provides significant promise for improving patency and long-term outcomes. In the years to come, further improvement in technology of the stent scaffolds and refinement of drug-eluting technology will further improve outcomes in endovascular interventions.

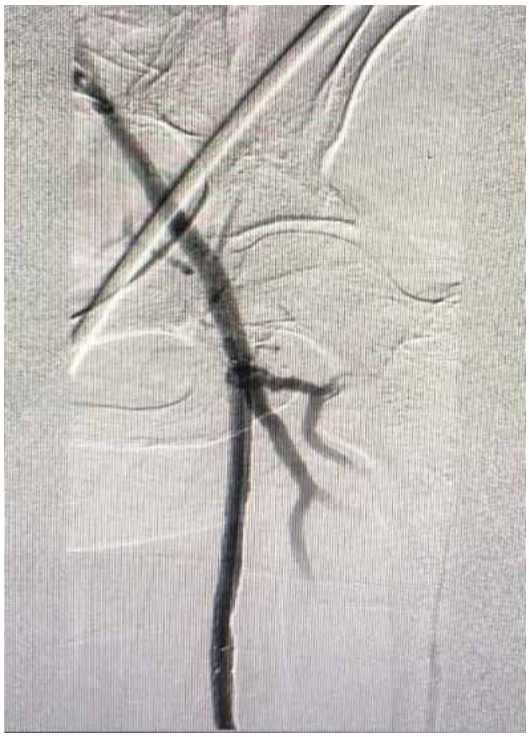

Figure 2. There is an example of retrograde approach of the SFA CTO (chronic total occlusion) intervention with PTA and two Zilver PTA self expanding drug eluting stents (post intervention).

6. Atherectomy

Treatment options for the PAD have significantly increased in number, but they remain limited in scope, as they are lacking substantial scientific data and large-scale randomized trials to help define the best therapy.

The majority of interventionalists use balloon expansion as a principal therapy which can or may not be followed by the stenting depending on weather the results of the angioplasty are satisfactory. This can be associated with vascular barotrauma leading to increase in incidence of restenosis and the need for re-interventions as the lesions are longer and heavily calcified. Stent use in SFA disease has shown significant improvement in vessel patency after intervention. [27, 28, 34]. However, the success rate of intervention decreases significantly as the lesions increase in size of more than 20 cm.

Changing arterial compliance through debulking specifically highly calcified plaques has been shown to be of benefit. Recent data suggest that atherectomy with or without adjunctive PTA and/or stenting has shown increased benefit [35].

Atherectomy devices remove plaque by physically shaving, drilling, or pulverizing by sanding the plaque resulting in modification of the vessel and its compliance. Atherectomy usually causes minimal trauma to the vessel and as such the incidence of acute complications including dissection and acute vessel occlusion may be reduced [36].

Initially, atherectomy devices were used in coronary artery disease without much success when compared to the contemporary bare-metal stents. Potential complication of atherectomy is the embolization of the debris distally. Shammas NW et al. performed a small study of 40 patients. In all patient that underwent atherectomy with SilverHawk device macro-embolization occurred. The study concluded that distal embolic filter protection is very effective in capturing macro debris and that is associated with good angiographic outcome. To determine the clinical outcome more randomized controlled studies need to be performed in the future [37].

Currently, there are several atherectomy devices available including directional, rotational, orbital, and laser atheroablative.

6.1. Laser atheroablative technique

Laser therapy received the FDA approval with the Laser Angioplasty for Critical Limb Ischemia (LACI) trial, where a total of 145 patients were enrolled. The diseased segments were equally distributed involving superficial femoral artery and infrapopliteal segments (41%) with 15% who had popliteal lesions. In this study, a 308-nm Excimer laser was used to ablate the plaque and thrombus, restoring the flow in diseased segments. Laser was delivered through a flexible fiberoptic catheter using short bursts of ultraviolet energy, which vaporized the plaque into small particles with minimal thermal injury in the surrounding tissues and lower chance for distal embolization [38].

In the CliRpath Excimer Laser System to Enlarge Lumen Openings (CELLO), Dave RM et al. evaluated the safety and efficacy of a modified laser catheter designed for the endovascular treatment of the PAD including the SFA and proximal popliteal artery. The study included 65 patients with intermediate claudication and stenotic lesion of more than 70% by visual assessment. Results revealed that laser ablation reduced the diameter stenosis from 77% to 34.7%. Patency rates were 59% and 54% at 6 and 12 months, respectively. There was significant functional status improvement with increased walking distance that was hemodynamically significant [39].

Laser atherectomy has shown to be effective also in patients with in-stent restenosis. Dippel EJ et al. conducted a multicenter, prospective, randomized controlled trial to assess the safety and efficacy of the Excimer laser atherectomy (ELA) in addition to PTA alone in patients who developed in-stent restenosis. The primary efficacy end point was TLR at 6 months follow-up. The primary safety end point was major adverse event (death, amputation or TLR) at 30-day post procedure. A total of 250 patient were included in the study, Rutherford class 1–4 and target lesion length was >4 cm. The lesion length was approximately 20 cm in both groups. ELA + PTA subjects demonstrated superior procedural success (93.5 vs. 82.7%; $p = 0.01$) with significantly fewer procedural complications and less target lesion revascularization (73.5 vs. 51.8%, $p < 0.005$) [40].

6.2. Rotational atherectomy

Rotablator system was first used in 1988 and it is currently available as Rotablator System and consists of an elliptical, nickel-plated, brass burr which is coated with 2000–3000 microscopic diamond crystals on the leading edge, and the burr rotates at 140,000–190,000 RPM. There are several available burr sizes available ranging from 1.25 to 2.5 mm. The majority of the debris, approximately 98%, is smaller than 10 micrometer, which traverses the microvasculature and is cleared by the reticuloendothelial system [41–43].

Clinical data currently lack any benefit in preventing restenosis in native and restenotic lesions. Rotational atherectomy is used to prepare a calcified lesion for stenting when a stent is not deliverable, or it cannot be properly expand [42].

In a single-center Excimer Laser, Rotablator Atherectomy, and Balloon Angioplasty study (ERBAC), a total of 685 patients were randomized to various atherectomy methods. RA had the greatest initial success, 89% in RA, 77% in Excimer laser, and 80% in balloon angioplasty. No differences were observed in major complications at the hospital and at 6 months follow-up. Revascularization of the original target lesion was performed more frequently in the RA group (42.4%) and the Excimer laser group (46.0%) than the angioplasty group (31.9%, $p = 0.0013$) [44]. Similar results were replicated in a multicenter, prospective trial of 502 patients, Comparison of Balloon Angioplasty versus Rotational Atherectomy in Complex Coronary Lesions (COBRA) [45].

Pathway Jetstream PV Atherectomy system consists of a single-use catheter with control pod and a reusable console. The system is indicated for both thrombectomy and rotational atherectomy. The catheter is advanced over a 0.014″ with a maximum rate of 1 mm/sec to avoid significant drops in rotational speeds; it has a front-cutting tip that makes it go through tight lesions. The electric motor spins catheters at 60–70 krpm, and for every 40 sec of treatment, a 10-sec pause is recommended. Jetstream expandable catheters 2.1/3.0 mm and 2.4/3.4 mm have a catheter tip that remains at a defined nominal diameter (2.1 or 2.4 mm) when spinning clockwise but expands to a maximum diameter when rotating counterclockwise. These sizes are recommended for larger-diameter arteries, typically above the knee. During atherectomy, the device offers a continuous active aspiration [46].

Clinical data are not very robust for the Pathway Jetstream atherectomy device as there are only small-sized studies performed. The largest study was conducted by Zeller et al. where 172 patients were included with femoropopliteal and popliteal lesions. The success rate was excellent (99%). Patients were followed up at 1 year and the restenosis rate as per arterial duplex ultrasound was 38.2%. Target lesion revascularization at 6 and 12 months were 15 and 26%, respectively [47].

6.3. Orbital atherectomy

Orbital atherectomy is an atherectomy device used for plaque modification to reduce the total atheroma burden, to change the arterial compliance, and to decrease vessel-wall trauma [48].

The orbital atherectomy device has an eccentrically mounted diamond-coated crown. The crown sizes include 1.25, 1.5, 2.0, and 2.25 mm. As the crown rotates, the centrifugal forces press the crown against the calcified lesion that is less compliant, while the healthy segment complies and moves away from the device reducing the risk for complications such as perforation. The small particles are so small that distal protection is not necessary. Short and slow runs are recommended of approximately 1–10 mm/sec to increase the efficacy and reduce the number of passages. Another advantage of orbital atherectomy over other atherectomy devices is the bidirectional treatment capability [49].

Clinical evidence for the orbital atherectomy use in peripheral artery disease has been shown in a serial of studies called CONFIRM registry series. A total of 3135 patient were included from over 200 centers in the Unites States from October 2009 to June 2011.

Results revealed that treatment with orbital atherectomy (OA) reduced pre-procedural stenosis from 88 ± 12% s to an average of 10% with adjunctive treatments, such as low-pressure BA. Further analysis showed that shorter spin times and smaller crown sizes significantly reduced procedural complications, which included slow flow, embolism, and spasm [50].

Orbital atherectomy can properly treat a calcified lesion, improving lesion compliance. OA also increases the luminal gain and by doing so decreases the need for high-pressure balloon inflation as demonstrated in COMPLIANCE 360°trial [51].

6.4. Directional atherectomy

There are two FDA-approved directional atherectomy devices, SilverHawk and TurboHawk. Both these devices are approved for peripheral vasculature use. SilverHawk is a forward-cutting directional atherectomy device. The device consists of rotating blade inside a tubular housing with a collection area. The TurboHawk device is similar in function but has four inner blades. Both devices come in various sizes to enable atherectomy in vessels with diameters of 1.5–7 mm as the device is advanced and though the lesion plaque is excised and packed in the nosecone. These devices have the advantages to remove eccentric lesions due to the advantage of directional control. Distal embolization remains a major disadvantage and the use of distal protection is recommended, especially in large and heavily plaques.

There is significant clinical data supporting the directional atherectomy devices in peripheral artery disease. In the TALON registry, a total of 601 patients were included with complaints of claudication and acute limb ischemia. The procedural success rates were high (over 97%), and a significant decrease in requirement for stent placement was noted after atherectomy (6.3%). One-year outcomes correlated well with angioplasty and stenting with free of target lesion revascularization in the 80% range. Cautious interpretation of the results is advised as this is an observational registry [52].

A serial of prospective randomized trials were done to assess efficacy of the directional atherectomy. McKinsey et al. enrolled 275 patients with femoropopliteal disease. Nearly two-thirds of patients had critical limb ischemia (63%). Limb salvage ischemia was over 90% at 1.5-year follow-up with a small percentage of patients (4.4%) requiring bypass [53].

OA efficacy was assessed in critical limb ischemia by Kandzari et al. where 69 patients were treated and prospectively followed for 6 months. Procedural success rate was very high (99%) with very low rates of target lesion revascularization (4%) [54].

In conclusion, endovascular therapy has become increasingly common in the treatment of obstructive SFA disease. With the advance in technology, PAD interventions can be performed with high success rate and relatively low clinical risk. New-generation drug-eluting stents have shown very promising results with better long-term patency. However, more randomized clinical trials are needed to prove the durability and safety.

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Chapter 3

Percutaneous Reconstruction Techniques: Popliteal Artery Approach for Chronic Total Occlusion of Superficial Femoral and Iliac Arteries

Omer Tanyeli

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.78045

Abstract

Peripheral artery disease (PAD) is one of the most common diseases affecting quality of life. Claudication is the most frequent sign. If left untreated, PAD may cause serious daily life disturbances and may cause extremity losses, especially in elderly and diabetic patients. Restoration of blood flow from the aorta to the femoral arteries and from the femoral arteries to the popliteal arteries necessitates complex operational procedures. Most of these patients have concomitant coronary diseases. In such patients, open surgical repair with vascular grafts by the aid of general anesthesia increases both mortality and morbidity. Although femoral arteries are the most common site for PAD, iliac impairment is not so rare. In patients with combined iliac and femoral artery diseases, popliteal artery approach is a safe and effective technique for percutaneous revascularization. In this chapter, we share our experience with interventional percutaneous revascularization through popliteal approach, mainly using drug eluting balloons and stents, by the aid of mechanical thrombectomy devices with the highlights of current literature review.

Keywords: peripheral artery disease, popliteal artery approach, stenting, balloon angioplasty, mechanical atherectomy, total occlusion

1. Introduction

PAD is third most common cause of cardiovascular mortality and mortality worldwide, following coronary artery disease and stroke [1]. Although the exact number of patients suffering from PAD is unknown, it is commonly agreed that there is a global increase in the amount of patients mainly by increased age and life expectancy of the populations, mainly

in underdeveloped countries. Fowkes et al. reported that there were 202 million people estimated to suffer from PAD, with a stronger change in the prevalence of low- and middle-income countries [1].

Elderly patients with diabetes mellitus and smoking habits are under great risk for PAD. Hyperlipidemia or hypertension is less likely to be the predisposing factors for the development of PAD.

Intermittent claudication (IC) is the most common symptom factor affecting quality of life. In order to improve walking distance, and prevent extremity losses, a wide variety of treatment strategies are offered including lifestyle changes, medical therapy, supervised exercise therapy, interventional procedures and surgical revascularization.

Ever since Seldinger discovered the needle-in, wire-in, needle-out, catheter in, interventional radiologists and cardiologists gained a favorable expertise not only in diagnosis of cardiovascular diseases, but also for treatment of vascular lesions. Over the past decade, with improvement of diagnostic procedures, catheter-based treatment strategies also increased and now almost became the first-line treatment strategy in almost all vascular diseases, mainly being performed by new generation qualified vascular surgeons and interventionists. Balloon angioplasty or stenting for a stenotic segment of the superficial femoral artery (SFA) became a routine process and endovascular procedures for complex chronic total occlusions (CTO) are more commonly being treated with interventional procedures using mechanical thrombectomy/atherectomy devices, which put the common surgical revascularization techniques in second order. In this chapter, we aimed to discuss the treatment of iliofemoral PAD, using combined endovascular treatment strategies, mainly focusing on the retrograde popliteal artery (PA) approach.

2. Peripheral artery disease

On the basis of anatomical and functional considerations, lower extremity occlusive PAD can be defined as atherosclerotic arterial disease and arterial narrowing, causing a mismatch between the blood supply and demand. Whatever is the cause, this mismatch results in symptoms including IC, exercise limitations, rest pain or tissue loss. These two definitions help divide the PAD patients into asymptomatic or symptomatic disease states [2]. About 10% of men at the age of 65 years are affected by atherosclerotic PAD. This ratio increases to 20% in men and women ≥75 years [3]. Besides its common nature, most of the patients remain asymptomatic and the disease is underdiagnosed. For every symptomatic patient with PAD, up to six patients are asymptomatic and miss the diagnosis. In a study of patients with PAD including 60-year-old men and women, Schroll et al. found that only 19% of patients were symptomatic [4].

2.1. The frequency of PAD location

Determining the location of PAD is crucial for decision-making and planning the treatment. The PAD may be classified according to the location of the involved arterial segment as aortoiliac, femoropopliteal and tibioperoneal segment. Location of PAD segment may vary

according to gender, associated disease, especially diabetes mellitus (DM) and the age group. Motsumi et al. reported that diabetic patients have severe occlusive disease involving the tibioperoneal segment [5]. Diabetic patients also have diffuse nature of PAD. Patients with DM, hypertension, dyslipidemia and smoking habits have significant occlusive disease of the femoropopliteal arterial segment. Smoking obviously increases the severity of arterial occlusive disease in the femoropopliteal segment or more proximal arterial segments. Diehm et al. reported that smoking had a higher relative risk ratio for severe involvement of the aortoiliac segment [6]. Interestingly, aortoiliac involvement in female diabetic patients was uncommon, irrespective of risk factor grouping and they had relative sparing of the arterial foot arch compared to their male counterparts [5].

When the frequency of the involved arterial segment in PAD was analyzed, researchers found that femoropopliteal location was the most common [6–8]. The involvement of femoropopliteal arterial segment varied between 47.3% and 77% in these studies. On the contrary, there are also a few studies reporting different results, mainly in the younger age groups. A study mainly focused on relatively younger age groups (<50 years) with early-onset PAD demonstrated that these patients had 65% aortoiliac disease [9]. In another study, common femoral arteries (CFA) were more commonly affected than the distal arterial segment (57.6% and 42.9%, respectively) [10]. In this study, older age, male sex, diabetes, heart failure and critical limb ischemia were more significantly associated with distal disease, whereas female sex, smoking, hypertension, dyslipidemia, coronary heart disease, cerebrovascular disease and chronic obstructive pulmonary disease were more significantly associated with proximal disease.

PAD resulting from atherosclerosis is a multisegmental disease in about two-thirds of symptomatic patients [11]. About 25–50% of patients have stenoses and/or occlusions in two or more segments [7, 12]. Knowing the fact that multisegmental disease affects about one in every 2–4 patients, determining the access site before any interventional procedure is very important.

2.2. Characteristics of Iliofemoral peripheral artery disease

Patients with PAD may have different symptoms depending on the anatomical location of the diseased arterial segments, onset of disease (acute or chronic) or presence/absence of the collateral circulation. Since the disease is progressive in nature, the patients may remain asymptomatic for years until the luminal obstruction is >50%. During this period, patients may have IC in strenuous exercise or may remain completely asymptomatic as stated earlier. As the disease progresses, and the luminal obstruction is >50%, patients may have progressively worsening IC, and the walking distance becomes to decrease. In following years, if the patient is left untreated symptoms intensify to rest pain, arterial ulceration, tissue loss or amputation.

There is a significant correlation between the severity of limb ischemia and the distribution of PAD. IC is usually associated with proximal lesions, and critical limb ischemia is associated with crural involvement. Proximal aortoiliac disease may cause thigh, hip, or buttock pain while walking and they are usually preceded by calf pain. Distal tibial or peroneal obstructions may result in ankle or foot pain while walking [13]. PAD patients with more severe and limb-threatening ischemia usually have multisegment involvement.

Patients with distal disease had poorer prognosis compared with patients without distal disease, independent of age, sex, comorbid conditions, medication (lipid-lowering and aspirin) use and resting ankle-brachial index (ABI), whereas patients with proximal disease showed no difference in prognosis after similar adjustment compared with patients without proximal disease. These findings suggest PAD is complex and heterogeneous and not a uniform entity [10].

The mortality for asymptomatic PAD is similar to that of mild to moderately symptomatic patients. Besides its beneficial effect on diagnosis of the disease, ankle-brachial index is also shown to correlate with the overall mortality of the disease [14]. The majority of these patients die of vascular causes such as cardiac, cerebrovascular, or other vascular diseases. The main reason for morbidity or mortality is either myocardial infarction or stroke. All-cause mortality is approximately 30% at 5 years, 50% at 10 years and 70% at 15 years [15]. In a population study, large-vessel involvement in PAD patients was significantly predictive of all-cause mortality in both genders with a relative risk of 4–5, independent of other cardiovascular risk factors. Isolated small-vessel PAD was unrelated to mortality. In that study, large-vessel PAD involved all arteries above the level of ankle [16]. Ogt et al. also found that the relative risk of mortality was elevated from 2- to 7-fold in men and women with multi- and unisegmental disease involving the aortoiliac and femoropopliteal segments. In the same study, the presence of tibioperoneal disease did not significantly increase mortality [8].

2.3. Diagnosis of iliofemoral peripheral artery disease

Depending on basic medical rules, the initial evaluation should include a careful history and physical examination. Knowing the fact that almost half of patients with PAD remain asymptomatic, suspicion of PAD for a clinician is very important. Shoes and socks should be removed for assessment of distal perfusion. Any signs of peripheral ischemia, peripheral pulses, skin color, toe nails, hair loss and trophic skin changes should be noted. Every sign of physical examination should be compared to the contralateral extremity. Abdomen should also be palpated for any potential abdominal aortic aneurysm. The blood pressure should be measured in both arms.

Upon suspicion and physical examination findings, referral to the vascular laboratory should be the initial step. The diagnostic tests should start by noninvasive methods. These noninvasive tests are also important for the follow-up of patients or disease progress.

The ABI is the single best initial screening test to perform in a patient suspected for PAD. A ratio of <0.90 is considered abnormal, with mild obstruction defined as a ratio of 0.71–0.90, moderate as 0.41–0.70 and severe when the ABI is <0.40. The higher arm blood pressure is used for the ABI ratio calculation [17]. The overall accuracy of the ABI to establish the diagnosis of lower extremity PAD has been validated with a sensitivity of 79–95% and a specificity of 96–100%, based on different studies [18, 19]. It is a reproducible technique, cheap and can also be used for screening and initial evaluation of target population, as well as assessment of disease progression. In patients with noncompressible arteries due to medial calcification such as elderly, diabetes and end-stage renal disease, toe-brachial index calculation may be helpful and values <0.7 are considered diagnostic for lower extremity PAD [20].

Treadmill exercise testing can be helpful, especially in patients with normal ABI during resting, such as in patients with isolated iliac artery stenosis. A decrease in ABI of 15–20% with

exercise is considered diagnostic for PAD. Climbing stairs, walking in the highway or 6-min walking test can also be performed not only for differentiation of claudication from pseudo-claudication, but also objectively assess the limitations of the patients and help to prescribe patient specific exercise programs. They are also important for patient follow-ups and disease progress [21].

Pulse volume recordings and Doppler waveform techniques are other techniques that can provide accurate information even in patients with noncompressible vessels. The normal waveform is triphasic. Loss of triphasic pattern and analysis of the peak velocity can localize the area of stenosis. They may be used to establish the initial diagnosis, assess the location and severity of PAD as well as follow-up of patients after any revascularization procedures [17].

Although they are not the first diagnostic test of choice in diagnosis of PAD, computed tomography angiography (CTA), magnetic resonance angiography (MRA) and digital subtraction angiography (DSA) are the other techniques that allow direct visualization of the vasculature in PAD patients.

CTA may be used with either intra-venous or intra-arterial contrast agents. The sensitivities and specificities are >95% for identifying stenosis >50% and for correctly identifying occlusions [22]. CTA produces images of vascular structures in cross-sectional slices that can be reformatted into three-dimensional angiographic-like images. CTA not only shows the intraluminal space, but also shows the surrounding tissue. For this reason, it visualizes calcification well, which is advantageous when considering revascularization strategies [23]. The main disadvantage is radiation exposure and the use of large volumes of iodinated contrast media, which limits its use in acute renal failure patients or patients with borderline renal function.

MRA is a useful diagnostic method in determining the location and stenosis severity in PAD patients. MRA may identify outflow vessels which may not be visualized by conventional angiography [24]. MRA has a high sensitivity and specificity for detecting acute occlusive disease when compared with DSA [25]. It is very useful for preoperative evaluation of the PAD patient in order to make a road-map, whether surgical or endovascular revascularization. **Figure 1** shows MRA of two different patients showing total occlusion of SFA.

MRA may also be used for postoperative follow-up of patients. A meta-analysis comparing MRA with catheter angiography demonstrated that sensitivity and specificity of MRA for detection of stenoses >50% were both in the range of 90–100% [26]. The main limitation of MRA is that it tends to overestimate the degree of stenosis because of turbulence; it cannot scan patients with pacemakers or defibrillators; metal stents or clips can obscure vascular flow; and use of gadolinium rarely may cause renal toxicity and nephrogenic systemic fibrosis in patients with elevated creatinine [17].

In our daily practice, there are some patients who are planned for endovascular interventions for critical stenoses, but not critically stenotic by DSA. Also, patients with previous stent in iliac/SFAs may also be misdiagnosed as occluded by MRA; that is why each patient needs a careful physical examination before MRA including comparative ABI. Duplex ultrasound scanning (DUS) may also give supportive data in these patients.

Contrast angiography provides detailed information about the vasculature, including minor collateral vessels, run-off and the flow speed, and is recommended as 'gold standard' method

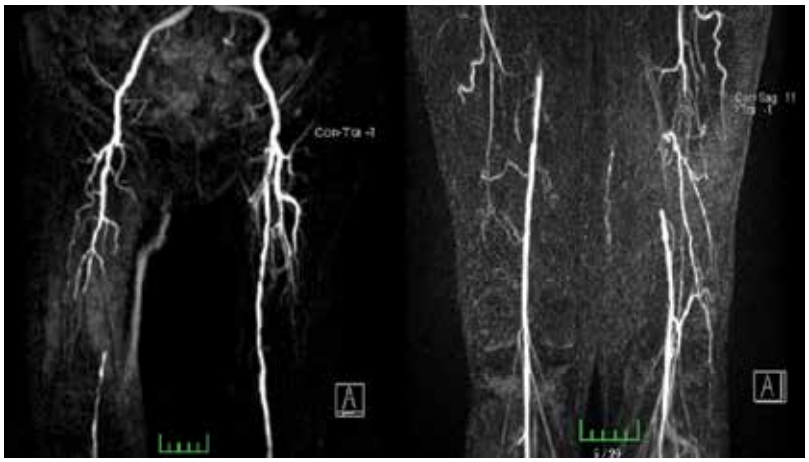

Figure 1. Contrast enhanced MR angiography, showing total occlusion of superficial femoral artery and well developed collateral circulation.

for evaluation of patients with PAD, especially when revascularization is considered. Image quality is enhanced by digital subtraction. The major advantage of DSA is the ability to selectively evaluate individual vessels, to obtain physiologic information such as pressure gradients and to serve as a platform for percutaneous intervention [23]. Angiography carries risk of any interventional procedure such as bleeding, infection, vascular damage, dissection, pseudoaneurysm formation and atheroembolism. Any of these factors can be reduced by experience of the interventionist [17]. As seen with other techniques, the use of contrast agent carries risk of contrast induced nephropathy, as well as anaphylactoid reactions. Angiography should not only be thought solely as a diagnostic method; at the same time, it also offers therapeutic options that are discussed later in this chapter.

Angiography, either noninvasive or invasive, should not be performed for the anatomic assessment of patients with PAD without leg symptoms because delineation of anatomy will not change treatment for this population.

3. Treatment options for iliofemoral peripheral artery disease

The management of lower extremity PAD is one of the most challenging problems for vascular surgeons/interventionists. As the population age increases and diagnostic tools improve, it is not surprising that the amount of patients seeking for treatment of PAD also increase day by day.

Treatment of any PAD, including iliofemoral PAD, can be classified into four categories including risk factor modification, exercise and cardiovascular rehabilitation, pharmacologic therapy, and invasive methods including surgery and interventional procedures [2]. Patients should not only be aware of their PAD, but also be informed and searched for other related diseases, including cerebrovascular and cardiovascular diseases. All the goals of these

therapeutic options are to improve symptoms and quality of life, at the same time decrease cardiovascular event rates.

3.1. Risk factor modification

Since cardiovascular events are the major cause of death in patients with PAD, modification of atherosclerotic risk factors should be the mainstay of risk factor modification. Smoking cessation and aggressive glycemic control in diabetic patients, both represent the most dominant risk factors for PAD, are very important [17]. Smoking cessation among patients with symptomatic PAD does not improve walking capacity, but may reduce the severity of claudication and the risk of developing critical limb ischemia [27].

In addition to smoking cessation and glycemic control in PAD patients, hyperlipidemia should be treated to reduce the risk of cardiovascular events in patients with atherosclerosis. Statin treatment is shown to have beneficial effects in reducing pain-free walking distance in patients with PAD, so that there is a positive effect on IC [28].

Hypertension is associated with a two- to three-fold increased risk for PAD. Hypertension guidelines support the aggressive treatment of blood pressure in patients with atherosclerosis, indicating PAD. In this high-risk group the current recommendation is a goal of <140/90 mmHg and < 130/80 mmHg if the patient also has diabetes or renal insufficiency [29]. Regarding drug choice, all drugs that lower blood pressure are effective at reducing the risk of cardiovascular events. Most patients will require multiple agents to achieve desired blood pressure goals [21]. The angiotensin-converting enzyme (ACE) inhibitor drugs have also shown benefit in PAD, possibly beyond blood-pressure lowering in high-risk groups [30]. Beta-adrenergic blocking drugs have previously been discouraged in PAD because of the possibility of worsening IC symptoms. However, this concern has not been supported by randomized trials, especially for cardioselective beta-blockers; therefore, beta-adrenergic blocking drugs can be safely used in patients with claudication [31].

3.2. Exercise and cardiovascular rehabilitation

In patients with claudication, there is a considerable body of evidence to support the clinical benefits of a supervised exercise program in improving exercise performance and community-based walking ability [21]. Apart from medical therapy, exercise significantly improves walking time and overall walking ability in patients with IC and should be considered as a primary efficacious treatment in PAD. Several studies have suggested that some level of supervision is necessary to achieve optimal results (general, unstructured recommendations to exercise by the physician do not result in any clinical benefit). In prospective studies of supervised exercise conducted for 3 months or longer, there are clear increases in treadmill exercise performance and a lessening of claudication pain severity during exercise [32]. Current ACC/AHA guidelines recommend a supervised exercise therapy as a first-line treatment for IC, as it is equally effective as endovascular revascularization in the treatment of patients with IC [33]. Whether asymptomatic or symptomatic, any patients taking support for PAD (either medical or surgical/interventional), exercise therapy (namely structured exercise therapy) should be considered, not only to improve IC, but also for motivation and promote risk factor modification.

3.3. Pharmacologic therapy

Apart from medical therapies used to modify risk factors for PAD (antihypertensive, antidiabetic and antihyperlipidemic drugs), there are some drugs that are shown to improve IC or prevent occlusion-reocclusion after surgery/interventional procedures.

Based on the currently available literature, all patients with PAD should receive antiplatelet therapy to reduce cardiovascular risk with a slight preference for clopidogrel monotherapy. Antiplatelet therapy with aspirin alone (range 75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke and vascular death in patients with symptomatic PAD [33]. The CAPRIE (clopidogrel versus aspirin in patients at risk of ischemic events) trial demonstrated a benefit of clopidogrel as compared with aspirin in cardiovascular risk reduction and bleeding events in a population of patients with symptomatic atherosclerotic vascular disease, including a subgroup of patients with symptomatic PAD [34]. However, there are two important subgroups that benefit from a different medical regime. Those receiving a venous bypass graft will have the most benefit when treated with a vitamin K antagonist and those receiving a below-knee prosthetic bypass graft will benefit the most when dual antiplatelet therapy (ASA and clopidogrel) [35].

Probably, the most effective pharmacologic treatment proven to be effective in relief of symptoms and improving IC in patients with PAD is cilostazol. ACC/AHA guideline strongly recommends the use of cilostazol in patients with PAD (class of recommendation IA) [33]. In a Cochrane review including 15 double-blind RCTs with a total of 3718 participants, cilostazol was associated with improvement in claudication symptoms but no changes in cardiovascular deaths or quality of life when compared with placebo [36]. The main limitation of the drug is congestive heart failure. Pentoxifylline is a xanthine and also acts as a nonselective inhibitor of phosphodiesterases, which causes an increase in intracellular cyclic AMP and decreased synthesis of tumor necrosis factor alpha and leukotrienes. It acts by improving red blood cell deformability, thus reducing blood viscosity as well as decreasing platelet aggregation and thrombus formation. By these properties, it was one of the agents used in PAD treatment. In a multicenter randomized control trial of pentoxifylline, cilostazol, or placebo for patients with moderate-to-severe claudication, there was no difference between pentoxifylline and placebo in the primary endpoint of maximal walking distance [37]. Therefore, pentoxifylline is not recommended as a treatment for claudication [33].

3.4. Invasive methods

An individualized approach to revascularization for claudication is recommended for each patient to optimize outcome. If a strategy of revascularization for claudication is undertaken, the revascularization strategy should be evidence based and can include endovascular revascularization, surgery, or both [33]. When deciding for an invasive method for treatment of PAD, patient's symptoms, localization of the affected arterial segment, patient specific factors including age, co-morbid diseases should be taken into consideration with a favorable risk–benefit ratio, with all combination therapies listed earlier.

In the last decade-or-two, endovascular procedures became one of the most popular concerns for treatment of PAD. There are numerous randomized clinical trials that compared endovascular procedures to various combinations of medical treatment with or without exercise programs.

When the aortoiliac disease is the concern, endovascular procedures are effective as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant aortoiliac occlusive disease (class of recommendation IA) [33]. The CLEVER trial enrolled only patients with aortoiliac disease and compared endovascular therapy to supervised exercise therapy and to medications alone. At 6-month follow-up, both the endovascular therapy and supervised exercise groups had improved peak walking time compared with medication alone, with a greater improvement in the supervised exercise group [38]. The ERASE trial randomized patients with claudication and aortoiliac (as well as femoropopliteal) disease to endovascular revascularization plus supervised exercise or supervised exercise alone. After 1 year, patients in both groups had significant improvements in walking distances and health-related QoL, with greater improvements in the combined-therapy group [39].

When the femoropopliteal disease is the concern, endovascular procedures are reasonable as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant femoropopliteal disease (class of recommendation IIa) [33]. There are a number of randomized clinical trials that showed short-term beneficial effects with endovascular treatment of femoropopliteal disease for claudication versus supervised exercise training or medical therapy, with benefit that diminishes by 1 year [40]. In a systematic review that included randomized clinical trials that enrolled patients with femoropopliteal disease, authors reported that endovascular treatment of claudication improved walking parameters and quality of life [41]. The durability of endovascular treatment for claudication is directly related to vessel patency. Long-term patency is greater in the iliac artery than in the femoropopliteal segment [33].

Since SFA and popliteal arteries are the most common sites of obstruction in PAD patients, when the surgery is the concern, femoropopliteal bypass is one of the most widely performed surgical processes in these patients with claudication. There is a clear and consistent primary patency benefit for autogenous vein versus to prosthetic grafts for popliteal artery bypass [42]. PTFE grafts should be preferred over Dacron grafts for femoropopliteal bypass when there is lack of autogenous grafts.

In this chapter, apart from the surgical revascularization, mainly endovascular treatment options for iliofemoral PAD and access sites will be discussed.

4. Endovascular management of iliofemoral lesions

Among those with appropriate indications for intervention, the procedure of choice, whether surgical or endovascular, depends on surgeon's/interventionist's experience, localization of the diseased arterial segment, anatomical suitability of disease and patient related factors, such as comorbid diseases. Most of the endovascular procedures are performed using local anesthesia on an outpatient manner.

Although the radiologists and cardiologists were the main pioneers of endovascular procedures, in the last decade, by the formation of hybrid operating rooms, vascular and cardiovascular surgeons became the leader of these interventional procedures. As a cardiovascular surgeon, in the last decade, we shared our patients with radiologists and cardiologists only for the reason that they had cath labs. The only way to re-face the patient was at the end of an unsuccessful attempt for percutaneous procedure, or a complication, such as rupture of the

artery, pseudoaneurysm formation, bleeding, or emboli and so on. All the interventions can be of-course performed by different departments, but any department should be capable of fixing their own complications, related to their interventions. In this decade, probably one of the most important advancement in PAD diseases was involvement of vascular surgeons in the world of endovascular and hybrid procedures.

Given the widespread availability of percutaneous procedures, major vascular society guidelines recommend initial percutaneous revascularization. The endovascular techniques for the treatment of patients with lower extremity ischemia include balloon angioplasty, stents, stent-grafts and plaque debulking procedures. Although long segment stenosis/occlusions, multifocal stenoses, eccentric and calcified lesions are more prone to surgical revascularization, use of total occlusion catheters, rotational thrombectomy/atherectomy devices made these complex lesions also treatable with endovascular procedures.

In general, the outcomes of revascularization depend upon the extent of the disease in the subjacent arterial tree (inflow, outflow and the size and length of the diseased segment). IN TASC-II guideline, 'A' lesions represent those which yield excellent results from, and should be treated by, endovascular means; 'B' lesions offer sufficiently good results with endovascular methods that this approach is still preferred first, unless an open revascularization is required for other associated lesions in the same anatomic area; 'C' lesions produce superior enough long-term results with open revascularization that endovascular methods should be used only in patients at high risk for open repair; and 'D' lesions do not yield good enough results with endovascular methods to justify them as primary treatment [21]. For treatment of TASC A lesions, the choice of treatment is endovascular, whereas it is surgery for TASC D lesions. Endovascular treatment is the preferred treatment for type B lesions and surgery is the preferred treatment for good-risk patients with type C lesions, which should be decided on a patient basis. The same is also recommended for femoropopliteal lesions.

The technical and clinical success rate of percutaneous transluminal angioplasty (PTA) of femoropopliteal artery stenoses in all series exceeds 95% [43]. Device developments such as hydrophilic guide wires and technical developments, such as subintimal recanalization, provide high recanalization rates in total occlusions of more than 85% [44]. The technique of subintimal angioplasty is not as dependent on length, but rather on the presence of normal vessel above and below the occlusion to allow access [45]. There is general agreement that for acute failure of PTA of an SFA lesion, stent placement is indicated.

The mechanism of endovascular treatment using balloon angioplasty and stenting is based on plaque disruption and displacement within the arterial wall. By this way, the atheroma is not removed but pressed or crushed by the balloon and redistributed inside and along the arterial wall. Endovascular atherectomy may be performed under local anesthesia using standard caliber arterial sheaths, ranging from 4 to 8 Fr, and provides the theoretical advantage over balloon angioplasty that plaque is removed rather than pressed against the arterial wall, and subsequent balloon dilation is optional depending on the debulking effect. This contributes to substantial luminal gain with less barotrauma even if postdilation is performed, decreasing the risk of dissection and/or neointimal hyperplasia, while avoiding stent placement [46]. In order to improve patency, the combination of lesion debulking using percutaneous

atherectomy and subsequent drug-coated balloon application has been implemented. Drug-coated balloons are proved to be an effective treatment option that does not require a permanent stent [47].

Atherosclerotic iliac artery disease is increasingly being treated with endovascular techniques. A number of new stent technologies can be utilized with high long-term patency, including self-expanding stents, balloon-expandable stents and covered stents, but comparative data on these stent types and in more complex lesions are lacking. Iliac stent choice can be largely categorized into choosing either a balloon-expandable or self-expanding stent based on lesion characteristics (i.e., calcified, fibrous, soft, eccentric, concentric, focal, diffuse, etc.), access site, introducer size, vessel tortuosity and lesion location [48].

For the last few years, our main strategy in treating iliac and femoropopliteal lesions are endo-first, if the lesion has suitable anatomy. For the patients with long segment stenosis and calcified lesions, we prefer rotational atherectomy for debulking of atherosclerotic plaque and then dilatation with drug-coated balloons. If there is a residual dissection, stenting is preferred. Mainly balloon inflatable stents are preferred for proximal iliac lesions, since the plaque over the iliac segments are generally stiff and prone to re-occlusion. For common and SFAs, our main preference is self-expanding nitinol stents, unless the problem is not solved by drug-coated balloons. As surgeons, we always should think of a possibility of reocclusion in these patients and that is why, stenting in the popliteal and distal CFAs should be avoided for alternative surgical sites.

4.1. Retrograde popliteal artery approach for femoral and iliac arterial lesions

To go inside a building, we should open the door first with the right key and in order to perform complex interventions, choosing the right access site is mandatory. There are several access sites described in the literature for endovascular procedures including ipsilateral retrograde common femoral access, ipsilateral antegrade common femoral access, superficial femoral access, contralateral common femoral access, retrograde popliteal access, pedal access, aortic access, radial access and so on. Whatever is the access site, the main goal is to approach stenotic/occluded arterial segments and perform endovascular interventions with success avoiding complications. Since PAD is not a uniform disease, and coexistence of femoral and iliac lesions are present in favorable amount of patients, retrograde contralateral common femoral access can result in procedural failure, especially in patients with unfavorable anatomy of the aortic bifurcation.

The SFA occlusions are generally managed by antegrade ipsilateral or retrograde contralateral femoral approach ending in intraluminal or subintimal recanalization of the vessel lumen [49]. In case of failure, a retrograde popliteal access is considered a valid alternative [50].

The retrograde popliteal approach is a type of subintimal arterial flossing with antegrade-retrograde intervention; it was first described by Tonnesen et al. in 1988 [51]. The main indications for this technique are a short SFA stump, flush occlusion or tandem common/SFA lesions and failure of antegrade approach. Also, coexistence of femoral and iliac lesions necessitates contralateral femoral approach; crossover in the abdominal aorta may complicate

the procedure in patients with angled iliac arteries and aorta. Also, in chronic total occlusions (TASC D), it may be rather difficult to crossover the aorta by the atherectomy devices, even if the patient had normal anatomy in the aortic segment. In SFA lesions, the access over the inguinal region may rather be hard, especially in obese patients.

For the abovementioned patients, popliteal access is a useful method for interventional procedures. The procedure begins in prone position. Prone position has the advantage of contralateral popliteal artery use, either for proximal visualization of the totally occluded artery, or crossover if the retrograde access is not successful. Puncture of the artery and replacement of sheath should always be made by the aid of an ultrasonography, since the popliteal vein is in close proximity to the popliteal artery and sometimes lies over the artery. Visualization of the vein and artery avoids iatrogenic AV fistula formation (**Figure 2**). Since majority of the patients have absent/weak popliteal artery pulses, ultrasonography aided catheterization should always be part of routine practice. After placement of 6–8 Fr sheath, a hydrophilic 0.0035 wire is advanced, and supported either by a slightly angled diagnostic catheter or total occlusion catheter. In total occlusions, the lesion is usually crossed intimally/subintimally by the aid of 6 Fr total occlusion catheter. Confirming that the guidewire is in the patent true lumen proximally, verification is made by angiography. In total occlusion of femoral/iliac arteries, our strategy is to make debulking of atherosclerotic plaque with rotational atherectomy devices and then use drug-coated balloons, or stents according to type and localization of the lesions (**Figure 3**).

A good preoperative evaluation is important before the procedure. Minimum popliteal artery diameter should be at least 4 mm. Local anesthesia should not be made too much in amount

Figure 2. Popliteal artery access using ultrasonography probe after application of minimal local anesthesia.

http://dx.doi.org/10.5772/intechopen.78045

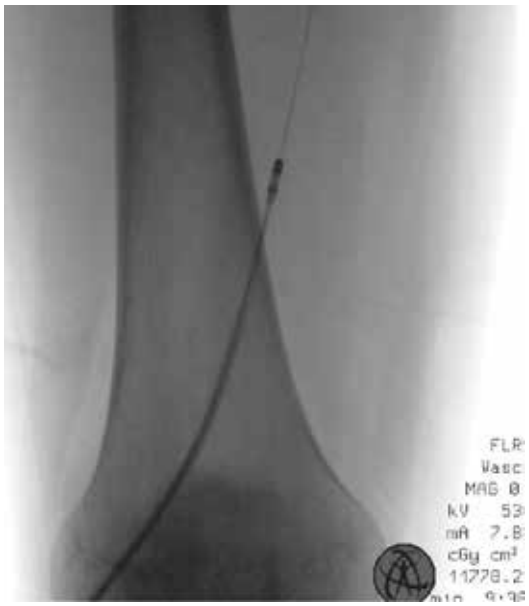

Figure 3. Rotational mechanical atherectomy catheter inserted through the 8F sheath over the popliteal artery in a retrograde fashion.

not to cause compression of the vasculature and obtain a clear image of ultrasound. Just a little amount of local anesthesia is usually enough; after insertion of the needle and guidewire, additional local anesthetic provides comfort of the patient.

Popliteal access is also advantageous in patients with occluded femoropopliteal artery bypass grafts. The atherectomy/thrombectomy can be made either from the native artery or the occluded graft, which usually results in high operational success in our cases. Videos (https://mts.intechopen.com/download/index/process/195/authkey/b9bb94b883d527ae-1b201a3ea2901c84) shows pre- and post-procedural angiograms showing total opening of SFA after rotational mechanical atherectomy and drug-coated balloons.

Subintimal guidewire extension and atherectomy usually results in residual dissection in the entry area; but since the direction of dissection is opposite to the direction of flow, in our opinion, this access becomes advantageous. As mentioned before, vascular surgeons should always leave a potential area for future surgical revascularization in the popliteal and common femoral arteries (CFA), after an eventful reocclusion of these segments.

The main disadvantage of this process is mainly based on the prone position of the patient. In complex cases, prolonged procedural times may disturb patients, especially if the patient has chronic obstructive pulmonary disease. Direct cannulation of the artery needs experience of ultrasonography and a learning curve in the very first few cases. Hematoma and post-procedural lack of compression may be overcome by routine use of vascular closure devices (**Figure 4**). Vascular closure devices are especially important when 6F or 8F sheaths are used for vascular access in the popliteal region; because, after the interventional procedure is completed, external compression may cause runoff failure, leading acute obstruction of the popliteal artery.

Figure 4. At the end of the endovascular procedure, popliteal artery is closed by vascular closure device to avoid compression.

Retrograde transpopliteal approach is an innovative technique that allows complex endovascular procedures, and should be a part of every vascular interventinal's skill set. Proper case selection, operator experience and appropriate technique are essential for clinical and procedural success.

5. Conclusions

PAD is one of the most common diseases affecting quality of life, especially in the elderly population. Since most of these patients are asymptomatic, a careful physician should always be suspicious about the diagnosis. Symptomatic patients should be encouraged to structured exercise therapy, in combination with risk factor modification, pharmacological treatment and invasive treatment strategies when needed.

Endovascular treatment options and the number of procedures dramatically increased in the last decade. A careful preoperative evaluation and plan should be made to achieve success in interventional procedures. Although femoral arteries are the most common site for PAD, iliac impairment is not so rare. In patients with combined iliac and femoral artery diseases, popliteal artery approach is a safe and effective technique for percutaneous revascularization. Interventionists should always have an alternative plan and access site in their reserve for the success of complex procedures.

Conflict of interest

None.

Notes/Thanks/Other declarations

Thanks Prof. Dr. Niyazi Gormus, for his expert opinion, patience and excellent guidance in our practice.

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Risk Assessment Peripheral Arterial Disease

Chapter 4

Cardiovascular Risk Evaluation in Patients with Critical Leg Ischemia before Vascular Surgery

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.78046

Abstract

Assessment of the role and investigation particularities (comparative and complementary aspects, hierarchies, preferential indication) adapted to the context of a global cardiovascular (CV) evaluation, including clinical elements, non-invasive and invasive imagistic examination in order to estimate the cardiovascular risk (CVR) and to define the revascularization therapeutic strategy in patients with critical leg ischemia (CLI). Complete and accessible evaluation involves accessible means of investigation like clinical exam, electrocardiogram, cardiac biomarkers, arterial, cardiac, and carotid ultrasonography which could be affordable in all cardiovascular departments. Non-invasive stress tests, coronary and arterial cervical angiography imaging leads in selected cases and where is possible to the identification of significant coronary and/or carotid lesions potential responsible for cardiac and cerebrovascular events after vascular surgery. The evaluation algorithm allows better risk stratification of patients with CLI in high and intermediate CVR. The "poly-arterial" status in patients with CLI changes the intervention management with a more intensive pre-operative medical treatment, while the coronary and the carotid arteries revascularization might precedes the peripheral arterial revascularization procedures, in order to reduce the CV risk status.

Keywords: critical leg ischemia (CLI), cardiovascular risk (CVR), poly-arterial (multi-arterial sites lesions), perioperative evaluation, non-invasive stress tests, cardiac biomarkers

1. Introduction

Atherosclerosis (ATS) is a systemic pathological process that affects coronary, cerebral and peripheral arterial circulation. Peripheral arterial disease (PAD) is a distinct athero-thrombotic syndrome marked by stenosis and occlusion of arterial beds [1]. A large proportion of PAD patients are not diagnosed before having a major ischemic cardiovascular (CV) event (MACE), which limits the use of medical therapies with recognized evidence of cardiovascular risk (CVR) reduction [2]. Even if claudication can remain stable over 10 years in 70–80% of patients, the prevalence of myocardial infarction (MI), stroke and CV death is high. PAD patients triple their risk of mortality from any other cause and have a six fold higher risk of death by coronary artery disease (CAD) than those without this ATS lesions. All these problems lead to repeated hospitalizations, low quality of life for patients and increased CV morbidity [3].

2. Predictors of perioperative cardiovascular risk

2.1. The risk of PAD patients in noncardiac vascular surgery

It is estimated that more than 200 million patients suffer a surgery intervention every year worldwide, and the proportion might increase up to 300 million in time. Most of these patients are elderly men, 25% of them having a high or intermediate CVR. The rate of MACE ranges from 11% in patients with one CV risk factor (CVRF) up to 33% in patients with four CVRFs. Perioperative mortality ranges from 0.9% in patients with one CVRF to 11% in patients with four CVRFs. Approximately 60% of patients with PAD have coronary artery disease (CAD), up to 25% of PAD patients have carotid-cerebrovascular atherosclerotic lesions, and the rate of MACE (MI, stroke and CV death) reaches 7% per year. The main causes of mortality in patients with PAD are due to cardiac events, coronary MI (60%) first of all, followed by major or fatal stroke (35%) and only a small proportion (15%) of these patients dies due to complications of critical peripheral arterial ischemia (by gangrene, septicemia and multiorgan failure) [4]. Along with coronary and/or cerebrovascular disease, the type of surgery is an independent predictive risk factor for death of PAD patients with multisite arterial lesions [5, 6]. This is why, patients undergoing vascular surgery have a higher risk of MI (31%), CV death (5%) than general surgery patients (3%) [4, 7, 8]. A good diagnostic and management strategy for PAD patients reduces vital CVR in terms of short outcomes and identifies patients with coronary and/or cervical arterial lesions at risk for long-term CV events. noninvasive tests can provide both diagnostic information (by revealing coronary ischemic heart disease (IHD) or cervical arterial lesions) and CVR prognosis in patients who undergo noncardiac surgery [4, 9, 10].

2.2. Benefits and limits of perioperative risk stratification

Cardiac risk stratification separates patients for vascular surgery into high-risk, intermediate and low-risk categories, adapting the management of perioperative therapy to their needs. Low-risk patients will be further investigated by completing noninvasive and invasive tests, while for high-risk patients, perioperative management primordially changes.

The major objective of CVR stratification is the reduction of perioperative global morbidity and mortality. Clarifying the patient's risk status allows the clinician as well as the surgeon to consent to a better informed patient. From a socio-economic point of view, reducing postoperative complications allowed to reduce perioperative care and treatment costs. The main impediment of perioperative risk stratification procedure is the duration, the cost and the number of investigational tests, which implicitly leads to postponing the intervention moment [4, 7, 8, 10]. And that could be done in elective surgery, but it seems to be quite difficult to be done in emergencies interventions.

2.3. Clinical elements of perioperative cardiovascular risk

2.3.1. Overview

Retrospective clinical studies have shown that a history of coronary artery bypass surgery (CABG), percutaneous transluminal coronary angioplasty intervention (PCI) or coronary angiography without significant lesions indicates a low risk for perioperative cardiac events. The risk is similar to that of patients without clinical signs of significant CAD. The term "protection" given by the presence of a coronary graft cannot be specified. Many studies in large groups of patients have shown the independent predictors of perioperative CVR: the history of MI, angina pectoris (AP), and ischemic ST-T changes on the electrocardiogram (ECG/EKG), as well as the clinical symptoms of congestive heart failure (HF) [9–11].

2.3.2. Several clinical risk assessment scores for postoperative cardiac events

The revised cardiac risk index (RCRI) is used by anesthesiologists and surgeons to assess the perioperative CVR in patients who undergo noncardiac surgery. Parameters included in the evaluation are age over 70 years, estimated risk of surgery, history or presence of IHD (MI or history of AP), congestive heart failure (HF), HT with signs of left ventricular hypertrophy (LVH), presence of Q waves or ischemic ST changes on resting electrocardiogram (ECG) cerebrovascular disease (CVD), the presence of DM (treated with insulin, additional risk) and renal failure (e.g., **Table 1**) [4, 12, 13]. The presence of more than one of these six independent predictors of cardiac complications following surgery is mandatory for further investigation. Patients who do not have active cardiac conditions are stratified into three groups by the RCRI: low (0 risk factor), intermediate (1–2 risk factors) and high (≥3 risk factors) [14, 15]. In a meta-analysis of 24 studies that reported the association of the RCRI with MACE or death in the hospital or within 30 days of surgery, the RCRI discriminated moderately well between patients at low versus high risk for cardiac events after mixed noncardiac surgery.

However, its performance was considerably diminished when it was used in patients who underwent vascular surgery and emphasized the necessity of development and validation of a suitable CRI for use in vascular surgery patients [14, 16, 17]. The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database derived from general and other specialty surgery patients have allowed the development of another risk model, in which five risk factors (basically the same from RCRI) were determined to be associated with MI/cardiac arrest following an operation [13]. In the VSG-RCI assessment (published in 2010 by Vascular Study Group of New England (VSGNE), additional

Clinical risk factors	Clinical elements	Active cardiac condition	Clinical presentation
History of ischemic heart disease (IHD)	Previous MI Previous positive result on stress test Use of nitroglycerin Typical angina pectoris ECG Q waves Previous PCI or CABG	Unstable coronary syndromes	Unstable or severe angina (CCS class III–IV) Recent MI (7–30 days)
History of compensated previous congestive heart failure (HF)	Previous pulmonary edema Third heart sound Bilateral rales Evidence of heart failure on chest radiograph	De-compensated HF	NYHA functional class IV worsening or new-onset HF
History of cerebro-vascular disease (CVD)	Previous TIA disease Previous stroke	Significant arrhythmias	High-grade atrioventricular block Symptomatic ventricular arrhythmias Supraventricular arrhythmias (including atrial fibrillation) with uncontrolled ventricular rate (HR > 100 bpm at rest) Symptomatic bradycardia Newly recognized ventricular tachycardia
Diabetes mellitus (DM)	With or without preoperative insulin therapy	Severe valvular disease	Severe aortic stenosis (mean pressure gradient > 40 mm Hg, aortic valve area < 1.0 cm^2 or symptomatic) Symptomatic mitral stenosis (progressive dyspnea on exertion, exertional presyncope, or HF)
Renal failure	Creatinine level > 2 mg/dL		

Adapted from [4, 13]. CCS, Canadian Cardiovascular Society; MI, myocardial infarction; HF, heart failure; NYHA, New York Heart Association; HR, heart rate.

Table 1. Clinical risk factor to predict MACE and active cardiac conditions to be evaluated and to be treated before noncardiac surgery.

risk factors were introduced: CVRF (increasing age, DM insulin-dependent, HT, smoking), clinical features (presence of aortic aneurysm, peripheral arterial ischemic symptoms, CAD, congestive HF, chronic obstructive pulmonary disease, elevated creatinine, abnormal cardiac stress test), previous CV medication administered (β-blockers long-term therapy, antiplatelet, statins) and revascularization interventions (carotid endarterectomy, peripheral arterial bypass, endovascular/surgical interventions for aortic aneurysm). The RCRI predicted risk after carotid endarterectomy reasonably well, but substantially underestimated the other

procedures for low- and higher-risk patients. VSG-CRI risk model predicted more accurately the risk of cardiac complications in vascular surgery patients than the RCRI, which underestimated in-hospital cardiac events in patients undergoing vascular surgery and that new VSGNE index was more accurate than the RCRI in predicting postoperative cardiac event. It should be noted that in this recent study only 45% of patients were evaluated by stress myocardial scintigraphy, the accessibility of the method still being limited [13, 18].

Generally, the type and the conditions of planned surgery cannot be fundamentally changed and can influence the postoperative CVR of patients. Urgent, prolonged (more than 5 h) and long hemodynamic stress (in major vascular interventions, intraabdominal and intrathoracic surgery) increase the risk of perioperative cardiac events. Peripheral vascular procedures present the highest risk (13%); the incidence of postoperative CV events could reach 10–15% [4, 7, 19].

2.4. Noninvasive cardiovascular parameters (biomarkers, coronary artery calcification)

Cardiac biomarkers have been studied for years in prediction of CV long-term outcomes, but less so for preoperative prediction. The most important and evaluated four biomarkers troponinI (TNI), N-terminal brain natriuretic peptide (NT-BNP), cystatin C, and C-reactive protein (CRP) significantly affected the prediction of death from CV causes. The statistical significance increased when the four biomarkers were incorporated into a model with established risk factors [20]. From six risk markers of interest (coronary artery calcium (CAC), carotid intima-media thickness (IMT), ankle-brachial index (ABI), brachial flow-mediated dilation (BFMD), CRP and family history of CAD, at a median follow up of 7.6 years, the CAC (had the highest predictive value), ABI, CRP and family history of CAD were independently associated with incident CAD [21, 22]. The addition of the degree of stenosis measured with computed tomography coronary angiography (CTCA), the presence of significant coronary artery stenosis (>50%) and/or multivessel CAD in completion with the CAC value and the RCRI significantly improved the predictive model for postoperative CV events [23]. Addition of CTCA determines a slight improvement in discrimination for CV death or MI. When added to the RCRI, information from CTCA is five times more likely to overestimate risk in low-risk individuals than to identify a previously misclassified high-risk individual. Thus, current data do not support CTCA as a first-line preoperative screening test for CAD in PAD patients (e.g., **Table 2**) [4, 24].

High CRP levels are positively associated with PAD, independent of smoking, and multiple other cofounders, demonstrating the important role of inflammation in ATS. High levels of inflammatory markers would identify vascular surgery patients at increased risk for adverse events (graft failure, MACE) after lower extremity bypass surgery. Among patients with an elevated CRP (>5 mg/L) before surgery, major postoperative MACE occurred in 60%, compared with a 32% rate in those with a baseline CRP < 5 mg/L (**Table 2**) [25].

High preoperative NT-BNP or CRP are independent predictors of perioperative MACE in noncardiac surgery; the addition of these two markers to the RCRI improves its predictive power for adverse events. There is a statistically significant association between an elevated preoperative NT-BNP level and various CV adverse outcomes within 30 days of surgery (composite of cardiac death, nonfatal MI and atrial fibrillation). NT-BNP concentrations of 99.5 pg./mL predicted cardiac events and 448 pg./mL predicted cardiac death (all-cause

Biomarker	Indication	Sensitivity	Specificity
NT-BNP	Obtain preoperatively in high surgical risk patients scheduled to undergo non-emergent vascular surgery	75–88%	62–100%
CRP		NA	NA
TnT		97%	54%
CAC	Evidence is currently lacking to recommend preoperative risk stratification with routine measurement	79%	61%

Adapted from [13].

Table 2. Indications and characteristics of various markers in preoperative cardiac risk stratification.

mortality in the short-, intermediate- and long-term postoperative periods). Over the threshold value of 448 pg./mL, NT-BNP had a positive predictive value of 100% and suggested that, if a preoperative NT-BNP level is in this vicinity, then it may be preferable to delay or cancel the procedure. Patients with high preintervention values of both CRP and NT-BNP are 10.6 times more likely to experience MACE than patients with normal CRP and NT-BNP values. Patients with a postoperative BNP ≥245 pg./ml or NT-proBNP ≥718 pg./ml had a significantly elevated risk for 30-day CV mortality, nonfatal MI, and cardiac failure. In addition, these postoperative elevations are able to predict long-term outcomes (i.e. ≥ 180 days after surgery) (e.g., **Table 2**) [26, 27].

Similar to postoperative troponin (Tn) levels, the current data for postoperative BNP suggest that it is the absolute postoperative threshold, rather than the increase in the BNP between the preoperative and postoperative period, that is associated with postoperative morbidity and mortality. Natriuretic peptides act as a cumulative marker of myocardial damage sustained during the perioperative period, possibly as a result of ischemic injury, volume overload or both. However, it remains unclear what the exact temporal relationship between postoperative BNP and Tn elevations is. In certain circumstances, it is possible that BNP elevation may precede Tn elevation, as may occur during fluid overload. In such cases, BNP elevations may identify patients at risk of subsequently developing myocardial injury and postoperative Tn elevation. Identification of patients at risk may provide a window for therapeutic intervention. It is likely that the more common scenario is postoperative BNP elevation that occurs together with, or shortly after, a postoperative Tn elevation. In these cases, elevated postoperative BNP may reflect the severity of myocardial injury and may prognosticate short- and long-term outcomes (e.g., **Table 2**) [26, 27].

In the perioperative period, it is clear that any Tn elevation is associated with an increased risk of death, even in the absence of a defining features (e.g., ischemic symptoms and ECG changes, evidence of MI on echocardiography) necessary for the diagnosis of MI. Owing to the effects of anesthesia, and widespread use of narcotics, the majority of perioperative ischemic events are clinically silent. In the Perioperative Ischemic Evaluation (POISE) trial, 65% of patients with a perioperative ischemic event did not experience ischemic symptoms [28]. The risk of death at 30 days was 9.7% in patients with a symptomatic MI and 12.5% in patients with an asymptomatic MI. Thus, the universal definition of MI may not be as sensitive in the perioperative period to detect ischemic events that are associated with poor, intermediate and long-term outcomes.

An isolated peak cardiac biomarker elevation (preferably Tn) with or without correlation with ischemia may be the most sensitive tool to detect perioperative ischemic events that are clinically important [29]. A peak postoperative TnT (>0.02 ng/ml) measured within the first 3 days after surgery is the strongest predictor of 30 days mortality and explained 41.8% of the deaths in population [30]. The current data suggest that the absolute postoperative threshold of Tn is a stronger independent predictor of postoperative MI and intermediate-term survival than the increase in the Tn level between the preoperative and postoperative period. Current data therefore suggest that a raised preoperative Tn level may identify patients who are at risk of increased short-term CV morbidity, mortality and long-term mortality (1 year after surgery, but no longer) due to his high sensitivity, but it may be an inappropriate additional test for improving preoperative risk stratification due to its poor specificity (**Table 2**) [26].

Preoperative cardiac biomarkers (especially BNP and Tn) evaluation adds incremental value to the risk stratification (by RCRI) for MACE (i.e. MI, pulmonary edema, CV death) and for in-hospital mortality [26]. While the body of evidence for the use of cardiac biomarkers for risk stratification is not extensive, the utility of assessing certain biomarkers in high-risk vascular surgical patients is suggested. A pharma-economic analysis of routine Tn surveillance in all patients who fulfilled the VISION study, based on a 25% relative risk reduction for vascular mortality and perioperative MI following the introduction of statin and aspirin therapy in high-risk patients who were Tn positive, found routine Tn surveillance to be cost-effective [30, 31].

2.5. Cardiac evaluation

2.5.1. Investigation of inducible myocardial ischemia

An ECG should be obtained in all moderate to high-risk vascular surgery patients and confers well-accepted prognostic information [11]. The two most common forms of stress testing are exercise ECG (not often feasible due to debility of many vascular surgery patients) and exercise or pharmacologic stress testing combined with imaging (e.g. dobutamine/dipyridamole stress echocardiography (DSE) and myocardial perfusion imaging scintigraphy (MPI)). There is an association between a positive test (ST depression) and the likelihood of postoperative cardiac complications [15]. Outpatient ECG monitoring is relatively affordable, but requires manual interpretation from the investigator, being time-consuming. The automatic or manual interpretation of the ischemic score depends on the correctness and the accuracy of the recorded ECG path. At a very variable percentage of patients (12–73%), recording irregularities are an obstacle to correct interpretation [32]. A study involving both noncardiac (general and vascular) surgery patients has not shown benefits in performing this type of ECG screening in preoperative monitoring [33]. Other studies focused only on patient groups in vascular surgery demonstrated both the positive and negative predictive value of the results of ECG monitoring of silent ischemia, but under the significance of the values provided by MPI. However, the combination of the two tests does not increase the predictive value [7, 28]. Ischemia and/or intra- and postintervention endocardial lesions (T-negative or ST-segment elevation) are more predictive for perioperative cardiac events (up to 85% of perioperative MI may also be preceded by episodes of ischemia-lesion on ECG), and the prognostic value increases if the cardiac Tn serum level reaction is associated [7].

2.5.2. Noninvasive clinical imaging tests for cardiac perioperative risk assessment

The American College of Cardiology (ACC) and the American Heart Association (AHA) as well as European Society of Cardiology (ESC) introduced guidelines to detect and manage perioperative cardiac risk and to prevent cardiac complications after vascular surgery [15, 19]. For preoperative noninvasive stress testing (NIST), the guidelines recommended that patients with active cardiac conditions should be evaluated and treated. NIST may be considered for patients with high or intermediate risk, if it will change management.

NIST include left ventricular (LV) function evaluation and inducible myocardial ischemia through ECG holter monitoring, ECG, echocardiography or scintigraphy coupled with exercise trial or pharmacological stress methods (**Table 3**). These noninvasive assessment tests should be able to detect cardiac abnormalities not revealed by clinical scores. The simple observation of some cardiac abnormalities does not necessarily means augmenting perioperative cardiac risk [32, 33].

NIST requires logistical and financial support. The PAD patients have less accessibility to MPI when compared to CAD patients. The interpretation of the investigation results in these studies is quite variable, which decreases the predictive accuracy. The explanations of these variable interpretations could be related to differences between the definition of fixed objectives, the follow-up strategies and the heterogeneity of the evaluated groups. Even though NIST are available and can be performed, they do not provide a "guarantee" for the perioperative period, as long as postoperative events have multifactorial causes that could not be accurately predicted [32, 33].

The perioperative period is characterized by myocardial ischemia due to hypercoagulability, increased consumption and oxygen demand, caused by catecholamine discharges, pain,

Tests	Prerequisites	Recommended indications
Electrocardiogram (ECG)	None in prior 3 months	CAD, PAD, CVD
	Perioperative risk death/MI >1%	Significant arrhythmia
		Structural heart disease
		Document baseline*
Echocardiogram	Potential to change management	HF with worsening symptoms
	Not for prognosis or as surrogate for exercise capacity	Dyspnea of unknown origin
		Clinical suspicion of structural heart disease
		HF or structural heart disease and no prior test within 1 year*
Non-invasive stress test (NIST)	Perioperative risk death/MI >1%	Unable to perform >4 METs based on subjective assessment or validated tool
	Elevated risk or known CAD	
	Potential to change management	

Adapted from [15].*Uncertain utility may be considered. CAD indicates coronary artery disease; CVD, cerebrovascular disease; HF, heart failure; MET, metabolic equivalents; PAD, peripheral arterial disease.

Table 3. Recommendations for preoperative cardiac investigations in vascular surgery.

anemia, anesthetic and surgical stress. Noninvasive clinical screening (via ECG, cardiac, carotid-vertebral and peripheral arterial ultrasound and where possible by NIST) coupled with cardiac Tn serum levels dosing increases the safety of postoperative evolution and improves the prognosis [34, 35].

Although available in many cardiology centers, stress tests could not be performed systematically in all presurgery intervention patients. Due to the pain caused by critical leg ischemia (CLI), 30–70% of PAD patients could not perform the exercise test; they are added to those who could not do it the same because of obesity, degenerative diseases of the hip and knee or postvascular sequelae. In this context, the results of the effort tests were inconclusive in several studies [7, 36]. For these patients, stress tests using pharmacological agents that increase consumption and demand for oxygen represent an alternative for detecting coronary ischemia. These stress tests are dipyridamole-coupled ECG, thallium myocardial scintigraphy and echocardiography coupled with dobutamine or dipyridamole. The presence of "reversible" segmental infiltration defects fixation, or alterations in segmental parietal kinetics has a predictive sensitivity with positive value greater than the presence of "fixed" defects (e.g., **Table 4**) [28].

Stress echocardiography with dobutamine (DSE) (or dipyridamole) has the theoretical advantage for evaluating both segmental ventricular parietal kinetics and altered LVF as determined by inducible myocardial ischemia. Most echocardiography stress studies conducted on vascular surgery patients suggested that DSE had a good negative predictive value, but the positive

Non-invasive stress tests	Advantages	Disadvantages
Stress ECG	Most affordable of the common testing modalities Widely available	Unable to use in many vascular surgery patients that suffer from claudication and poor functional capacity, as target heart rates cannot be achieved. No additional information about cardiac function that can be seen with cardiac imaging is provided
Stress echocardiography (dobutamine) DSE	If pharmacologic stress testing is necessary, may be preferred in patients with known bronchospastic lung disease or significant carotid stenosis. Preferable choice when any additional information about left ventricular function and/or valvular heart disease is desired. Shorter testing time with results available sooner. No ionizing radiation.	Dobutamine has the ability to induce arrhythmias and increases in blood pressure and/or myocardial contractility; avoid in patients with known arrhythmias and symptomatic or large aortic aneurysms
Myocardial perfusion imaging or scintigraphy (MPI with dipyridamole/thallium)	If pharmacologic stress testing is necessary, may be preferred in patients with known arrhythmias and symptomatic or large aortic aneurysms. Preferable for the assessment of myocardial viability in patients with known left ventricular dysfunction, where the extent and severity of inducible ischemia is of importance.	Dipyridamole may induce bronchospasm or decreases in blood pressure; avoid in patients with bronchospastic lung disease or significant carotid stenosis. Longer testing time and delay for results to be available. Ionizing radiation. Failure to detect global ischemia

Adapted from [13].

Table 4. Comparison of noninvasive stress testing modalities.

predictive value was moderate. This does not increase the discriminatory value of the clinical criteria and does not change the appropriate risk group ranking after the RCRI score. In patients with one or two positive cardiac markers, the negative value of DSE was confirmed by the absence of postoperative cardiac events, while a positive result was followed by an incidence of up to 5% of cardiac events postoperative (MI, sudden death), so preoperative DSE offered no incremental value for determining postoperative adverse cardiac outcomes [7, 28, 37]. The second multicenter Dutch Echocardiographic Cardiac Risk Evaluation study showed no difference between the intermediate risk patients with positive NIST results group and negative results group in cardiac death or MI at 30 days after surgery (1.8 vs. 2.3%) (e.g., **Table 4**) [38].

Myocardial perfusion imaging (MPI) scintigraphy combined with pharmacokinetic stress test and EKG with dipyridamole are most used today in centers that benefit from this availability. Despite the initial expectations of better characterization and stratification of patients, especially from groups initially assessed as having intermediate or low risk for postoperative cardiac events, the results were not what they expected. Stress MPI has a relatively high sensitivity for the prediction of cardiac complications, but the specificity of this method is less satisfactory. Preoperative MPI has a high negative predictive value, but it has not proven to be sufficiently sensitive, and the benefit of MPI was unproven in low-risk patients and probably not cost-effective. There was no association between reversible defects on dipyridamole stress MPI and adverse cardiac events in moderate-risk patients undergoing elective vascular surgery. Based on the scintigraphy results, previously patients in the low-risk group switched to the intermediate risk group, but the rate of postsurgery intervention cardiac events do not change significantly, indicating the limited positive predictive value of these tests and proving no independent prognostic value superior to clinically stratified risk [7, 28]. Information about myocardial perfusion does not accurately predict adverse cardiac outcomes (e.g., as prolonged myocardial ischemia, MI, congestive HF and severe ventricular tachyarrhythmia) following univariate and multivariate analyses. The best correlates of cardiac complications were documented evidence of CAD and age greater than 65 years (e.g., **Table 4**) [12, 24, 39].

Two important questions remain unanswered related to the patient at risk: which stress test is best for which patient and what interventions outside of best medical management are of benefit to reducing perioperative ischemia events. No large head-to-head analyses of DSE versus MPI have been performed, although two well-known meta-analyses have compared the different modalities. DSE showed a positive trend toward better diagnostic performance than the other tests. Relative to MPI, DSE had a similar sensitivity, but significantly greater specificity (70% vs. 49%) (e.g., **Table 3**). Comparison with summary receiver operating characteristic analysis between all modalities revealed a trend toward better performance with DSE, but this was only significant when compared with MPI. DSE has better negative predictive value characteristics than MPI. In addition, a moderate-to-large perfusion defect by either DSE or MPI predicts postoperative MI and death, but DSE is slightly superior to MPI in predicting postoperative cardiac events [24, 39].

A typical pattern has emerged with stress testing for risk stratification prior to surgery; the positive predictive value is usually very low, and the negative predictive value is typically high. Routine preoperative NIST is not necessary in all patients undergoing revascularization for CLI, especially for patients in the low-risk group and for those undergoing endovascular

http://dx.doi.org/10.5772/intechopen.78046

treatment [40]. Widespread use of NIST in assessing the risk of perioperative CV complications remains controversial due to the low predictive value that affects the accuracy of the information. Therefore, the implications for CV risk stratification remain unclear. Even with the reported subtle differences between MPI and DSE, the fact remains that current guidelines do not distinguish between one or the other NIST for the preoperative workup of surgical patients. In line with current joint guidelines, we would recommend that surgeons take into account the availability and expertise in interpretation of the varying modalities and patients specifics at their respective institutions when deciding which test to obtain (e.g., **Figure 1**) [13]. A reversible defect on NIST is considered a predictor of postoperative MACE, and possible revascularization might be recommended. Some authors have suggested coronary angiography as a routine screening test, due to the significant prevalence of coronary involvement in vascular patients. Because coronary angiography is an invasive method with a risk of up to 0.05%, it was not used in studies as a routine examination in perioperative RCV assessment in noncardiac surgery patients. Last data suggested perioperative MI is quite common in

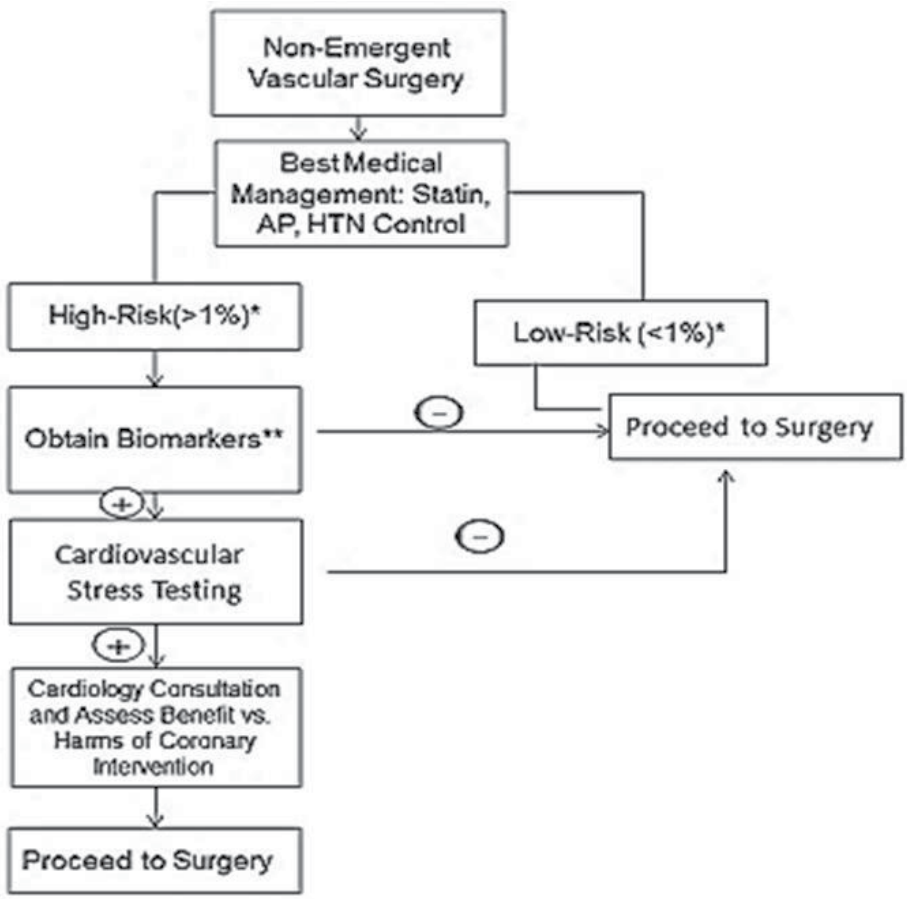

Figure 1. Suggested algorithm for preoperative optimization in vascular surgical patients. AP—Antiplatelet therapy; HTN—Hypertension. Adapted from [13].

nonvascular surgical patients, vascular patients being relatively protected by cardiovascular medication previously administered, and that postoperative events such as anemia play a major role in postoperative MI [41].

2.5.3. Cardiac ultrasound evaluation in perioperative assessment of PAD patients

With cardiac ultrasound (US) (or echocardiography), we can evaluate both the function and the morphology of the heart. The presence of LVH is associated with an increased risk of CV morbidity and all-cause mortality, which emphasizes the importance of diagnosis. The quantitative evaluation of the LV systolic function by LV ejection fraction (LVEF) is a simple and specific predictive index in relation to clinical utility [42]. End-systolic LV volume is an independent predictor of survival in CAD and LVEF has prognostic value for survival in post-MI patients. The presence of diastolic dysfunction represents an early indicator of LV function impairment. Although that high mortality of PAD patients was mainly attributable to coexisting coronary or cervical arteries disease, the prevalence of US abnormalities in patients with peripheral arterial ischemia was not systematically studied. Asymptomatic LV dysfunction is predictive for short- and long-term perioperative CV events in vascular surgery patients; therefore, the echocardiogram should be routinely performed in surgical patients for stratification of CV risk, even in the absence of HF symptoms [43].

The prevalence of CVRF (smoking, DM, dyslipidemia, HT) in PAD patients causes, in addition to peripheral arterial lesions, coronary arteries and myocardial involvement with ischemic, hypertensive and/or diabetic heart disease, aortic and mitral valve calcifications and sometimes myophatic evolution through dilated cardiac disease [44–46]. In PAD patients were found high prevalence of clinically significant cardiac US changes (61.6% vs. 35.3%), especially related to the LV dysfunction and the presence of aortic stenosis (AS) compared to patients without PAD. The presence of PAD is shown to be an independent predictor of LVEF <50%. In PAD patients, MI and HF are the main causes of mortality [47]. PAD patients develop a significantly higher degree of LVH compared with patients with the same means BP but with no PAD. By cardiac US examination, LVH was found in 75% of patients with HT, CAD and PAD and in 46% of patients with HT and CAD but without PAD, respectively. LVH was found in 93% of PAD patients, with ABI <0.6, and 62% of patients with ABI between 0.6 and 0.9 [43, 47–49]. PAD patients with CLI have higher CV morbidity than stable PAD patients. US evaluation is useful in defining the group of patients with low CV risk, in which can be performed with relative safety the revascularization of the limb by interventional/surgery procedures. In the case of the intermediate risk group, additional CV risk assessment tests are required [44–50].

2.6. Perioperative cardiac management strategies

2.6.1. The impact of perioperative risk stratification in the management of PAD patients

Approximately 10% of general surgery patients are included in the high-risk surgical perioperative group after the standard clinical and noninvasive assessment. But for vascular surgery patients, the percentage of high-risk patients may increase by 10–20%. From these, 5–10% may be eligible for myocardial revascularization (PCI or CABG) [7]. In vascular surgery patients in intermediate or low perioperative risk groups, it is advisable to perform NIST. It is possible,

however, that NIST does not provide additional predictive perioperative risk elements. Also, these tests do not provide information about cerebrovascular ischemic risk, derived from cervical arterial lesions, almost equally founded as coronary involvement in vascular surgery patients [7, 29]. Clinical judgment is important in assessing the balance between the relative urgency of identified cardiac and noncardiac surgery problems. A relatively small proportion of surgical patients require urgent preoperative treatment of cardiac conditions: congestive HF, life-threatening arrhythmias or acute coronary syndrome (ACS) (recent MI with significant evidence of ischemic risk or unstable, severe AP). However, there are situations in which the surgical situation with an important vital risk imposes the operative decision, even under an incomplete cardiac evaluation [7, 29].

2.6.2. Impact of coronary revascularization decision on noncardiac surgery patients

Patients in noncardiac surgery are at risk of major perioperative cardiac events (sudden cardiac death, cardiorespiratory arrest, MI). In these patients, the in hospital mortality rate is among 15–25%. Patients who underwent a postsurgery intervention cardiac arrest have a mortality rate in the hospital up to 65% and represent a risk factor for cardiac death within the next 5 years postoperatively. Perioperative MI is an independent risk factor for the risk of CVD and the increase incidence of a new MI over the next 6 months postoperatively [7]. This is why the concern is both for the most discriminatory assessment of noncardiac surgery patients in different risk groups, as well as for finding the best prevention strategies (interventional, medical, etc.) for perioperative CV events. By preoperative coronary angiography, the prevalence of CAD ranged between 50 and 80% and is dependent on the specific distribution of the PAD. It is also clear that periprocedural myocardial ischemia, even non-ST segment MI and Tn leaks, confer a significant 26–55% decreased survival through 5 years, supporting the impetus for careful patient preparation [13].

In retrospective studies, for both vascular and nonvascular surgery patients, the "protective" effects of coronary revascularization in reducing perioperative MACE were controversial [7]. "Prophylactic" preoperative myocardial revascularization of significant lesions could reduce perioperative coronary complications in patients with unstable CAD (ACS) and high CVR. There is a significant difference in mortality among high CVR patients who underwent coronary revascularization prior to noncardiac surgery (0.9%) compared to high CVR patients who did not undergo coronary revascularization procedures (2.4%) [7]. Coronary revascularization performed prior to noncardiac surgery has as a primary objective the reduction of CV mortality in the long-term outcome and as a secondary objective, the reduction of CVR in patients with high coronary risk: unstable refractory AP, left main coronary artery stenosis, coronary multivessel significant lesions, including anterior descendent artery (ADA) and altered LV systolic function. Patients who underwent myocardial revascularization before noncardiac surgery had a lower rate of long-term postoperative cardiac events (up to 5 years after noncardiac surgery). The lowest incidence of CV events in long-term outcome after noncardiac vascular surgery was observed in the group of patients with PCI versus revascularized patients by CABG [50, 51].

The Coronary Artery Revascularization Prophylaxis (CARP) trial showed no difference in the rate of postoperative MI (defined by elevated Tn level) (12 vs. 14%) in 30-day mortality, and MACE and mortality at 2.7 years (22 vs. 23%) in patients scheduled for vascular surgery

with coronary artery revascularization before surgery compared with patients with no revascularization before surgery, but there was a statistically significant survival benefit at 4 years (87% vs. 70%) that persisted up to 8 years. The CARP trial focused on patients who had stable CAD and those without left main coronary disease or significant valvular heart disease. Time to vascular surgery was significantly longer in the revascularization group [52, 53]. Although this evidence is encouraging, caution is warranted. Of note, excellent adherence with cardioprotective drugs was documented. At least one large database review of nonvascular surgical patients concluded opposite findings, suggesting a benefit of revascularization, so the controversy remains open [54].

A prospective study included patients evaluated before vascular surgery by MPI to complete the coronary angiography indication followed by myocardial revascularization by PCI and/or CABG. The results of MPI have increased the rate of coronary revascularization from 4.1% to 14.7%, without significantly improving postoperative MACE (MI, sudden cardiac death in the first 30 days after surgery intervention). However, it should be noted that the patients included in the study had one or two coronary vessels significant lesions with preserved LV systolic function and with optimal medical therapy. Patients with CAD and with severe impairment of LV systolic function, unstable AP and AS were not included. In vascular surgery patients having three coronary vessels significant lesions, there was a slight decrease in the incidence of perioperative cardiac events in myocardial revascularized patients before vascular surgery (43%) versus those treated by standard medical therapy (33%) [7]. Therefore in the coronary revascularization decision made prior to noncardiac surgery, three elements should be considered: the coronary risk of the patient, the risk of bypass surgery and the risk of noncardiac surgery. These results do not suggest that there are benefits in prophylactic coronary revascularization in patients with stable CAD regarding the short-term evolution after vascular surgery intervention [50, 51].

One of the main objectives of preoperative cardiac evaluation should be the identification of patients with high-risk coronary anatomy, amenable to revascularization, by an appropriate and discriminatory noninvasive/invasive cardiac evaluation. Once identified, the next question that needs to be answered is what the best revascularization strategy would be, CABG or PCI? The indication and the accomplishment of PCI before noncardiac vascular surgery are directed toward patients with high coronary risk prior to noncardiac surgery. PCI has the advantage of a low periprocedural risk (0.01%) and avoids the stress of CABG. The disadvantage of the PCI is that some lesions could not be accessed by angioplasty and should be resolved later by CABG [7, 50, 51]. Long-term outcomes appear to be better in patients undergoing CABG when compared to PCI, but incomplete revascularization after PCI, impact of stent-related complications and progressive occlusive CAD should be considered while evaluating the disadvantages of PCI over CABG. The heightened thrombogenic potential of newly implanted stents and prothrombotic state induced by the surgical stress increase the risk of in stent thrombosis. Premature discontinuation of antiplatelet therapy in patients with bare metal stents (BMS) or drug eluting stent (DES) is associated with a high rate of stent thrombosis and perioperative mortality. Elective surgical procedures that carry a potential for increased perioperative bleeding should be postponed until a minimum course of dual antiplatelet therapy (DAPT) has been completed. In patients presenting for emergency

noncardiac surgery after stenting, consideration should be given to the risk of interrupting thienopyridine antiplatelet therapy compared with the risk of bleeding from surgical procedures, to continuation of aspirin in the perioperative period and to restarting thienopyridine as soon as possible [4].

Coronary revascularization is not recommended before surgery for patients with stable CAD in both ACC/AHA and ESC guidelines for the management in patients undergoing noncardiac surgery and it is recommended only in circumstances where it would be indicated even in the nonoperative setting. In general, CABG is recommended for left main disease, triple-vessel disease, complex anatomy or high-risk comorbidities (e.g. diabetes). Given the uncertain benefits of preoperative PCI for improving outcome after noncardiac surgery, current guidelines suggest consideration of PCI only for patients with left main disease whose comorbidities preclude CABG and for patients with unstable CAD (e.g. ST-elevation MI, non-ST-elevation ACS) who are appropriate candidates for emergency or urgent revascularization. If revascularization by PCI is considered, BMS is preferred over DES for vascular surgery patients given the time pressure to proceed with vascular surgery [15, 19].

The additional risk of anesthesia and intervention stress in noncardiac surgery patients who also have simultaneous cardiac problems should be noted. Even under these conditions, the idea of "prophylactic" coronary revascularization, in all cases, could not be accredited to patients who undergo vascular surgery, on the premises that they have multisite arterial lesions and therefore they also have coronary ATS [36]. Probably only prophylactic coronary revascularization of significant lesions in confirmed CAD could prevent perioperative complications in noncardiac surgery patients [8].

In the Reduction of Atherothrombosis for Continued Health (REACH) Registry, more than 50% of PAD patients had a concomitant CAD [2]. This means that modification of ATS risk factors is important in the long term and perioperative CVR is high in the short term [55]. Patients with high CVR should benefit from a sustained medical treatment and control of CVRF, considering the context of a possible myocardial revascularization intervention by PCI or by CABG, as well as the perspective of a future vascular surgery. Patients at risk of having CAD (regardless of the risk group) should be given control of blood pressure, serum cholesterol (via statins), cardiac compensation (angiotensin converting enzyme inhibitors (ACEI), diuretics) and arrhythmia (β-blockers, amiodarone). Numerous scientific studies have demonstrated the beneficial role of β-blockers, antiplatelets, ACEI and statins in reducing perioperative CV mortality in patients undergoing noncardiac vascular surgery. Statins and antiplatelet therapies are also involved in ATS plaque stabilization and improvement of endothelial dysfunction [56–58].

2.7. Cervical arterial ultrasound evaluation in perioperative assessment of PAD patients

With the increase in the use of cardiac and arterial ultrasound (US) in assessing the patient with suspected or known PAD, the diagnostic and prognostic accuracy of these explorations has increased, the sensitivity and specificity of US detection cervical arterial lesions may reach 95%. Noninvasive US methods can also be applied to a wide range of patients including those

at high risk for myocardial stress testing. With respect to CVD, a history should ascertain any previous stroke or transient ischemic attack, as well as detail the associated presentation and deficits. It is important to document the etiology to distinguish ATS carotid stenosis from cardio-embolic disease [44].

Carotid intima media thickness (IMT) measured by US is a noninvasive predictive marker independent of the onset, progression and extension of ATS disease, demonstrated in numerous studies. The increase in carotid IMT is associated with a higher incidence of coronary events and multisite ATS lesions [59]. Increased IMT has common risk factors with the onset and progression of coronary and cerebrovascular ATS lesions (HT, DM, dyslipidemia, smoking) [60, 61]. Furthermore, increased IMT demonstrates good reproducibility for both the progression and regression of ATS disease and has been validated as a vascular marker of ATS evolution in numerous clinical trials. At the same time, invasive studies have shown that treating CVRF for CAD can also significantly reduce progression of IMT [62, 63]. Carotid and femoral IMT thickening are associated with the presence of CVRF; the occurrence of CV events is an indicator of the presence of PAD. It has been shown that these risk factors and CV events are significantly linked to increased carotid and femoral IMT. The treatment of CVRF is associated with a decrease in the progression of IMT thickening, parallel to the reduction of CV events and an improvement in the symptoms associated with PAD. This finding is particularly evident in the context of hypolipemiant therapy. IMT, as an additional predictor of CVR, may influence the decision of therapeutic intervention by medication [59–63].

Significantly elevated IMT values were seen in PAD patients at femoral artery, simultaneous with carotid artery, which allowed the conclusion that the presence of PAD is associated with morphological alterations and dynamic variations of both the femoral and the carotid artery walls. DM patients with PAD had a significantly higher IMT at the carotid bifurcation and at the distal common carotid artery, relative to those without PAD. Thus, carotid IMT may be a marker of ATS with different localizations in patients with type 2 DM and reflects morphological and hemodynamic similarities between arterial beds [64]. Today, IMT is one of the most commonly used parameters of noninvasive assessment of CV-ATS risk. In the initial stages, clinical latency of ATS, the increase of carotid IMT over normal value, often is an indicator of the asymptomatic arterial ATS lesions as well as an accompanied predictor for the increased risk of future CV events in already symptomatic arterial ATS territories [1, 65]. The amount of carotid IMT in PAD patients is correlated with body mass index (BMI), ABI, serum LDL-cholesterol and the number of arterial cervical ATS plaques. These results support the hypothesis that ATS is a systemic, generalized disease, leading to functional and structural changes in each of the segments of the arterial system, as confirmed by many other studies that described the concomitant occurrence of carotid, coronary and peripheral arterial ATS disease. Up to 81% of PAD patients with increased IMT had angiographic coronary artery lesions, while 57% had carotid ATS plaques. Therefore, there is a statistically significant correlation between increased carotid IMT and the severity of CAD and also the presence of carotid ATS plaques and PAD clinically manifested which are positive predictive factors for the presence of CAD [1, 65].

PAD patients had advanced cervical arterial ATS lesions expressed both by a higher IMT and an increased prevalence of ATS plaques. Stenotic and occlusive ATS is a systemic phenomenon commonly coexisting in several arterial territories (coronary, carotid, peripheral

arteries), often symptomatic in one of the arterial areas and asymptomatic in other affected arterial areas [44–46]. There are fewer studies that investigated the lesions in the cervical arterial system in patients with PAD, compared to the large number of studies investigating the coronary-carotid relationship [65]. Noninvasive vascular imaging, especially CV ultrasound, plays a particularly important role in the carotid evaluation system, and in some aspects (the morphological characterization of the ATS lesion and the possibility of analysis in multiple "nonstandardized" incidences) is superior to conventional angiography allowing accurate measurement of the functional diameter and the lumen area of the vessel, precise localization and dimension (thickness/length/extension and volume) of the ATS plaque, the ecostructure and the surface characterization of the ATS plaque and defining the type of vascular remodeling. Thickness, ecogenicity and endoluminal surface of the ATS plaque are the first features related to a possible instability characterized by the US assessment of vascular lesions [67, 68].

There are studies that argue that US technique overestimates the severity of carotid stenosis compared to angiographic assessment, but these results depend on the US way of quantifying stenosis. The two-dimensional US combined with color and pulse doppler modules generally leads to superimposable results with angiographic quantification [68–71]. Carotid angiography is indicated in selected cases and, particularly in cases where US is difficult to perform and poses diagnosis problems, shows particular aspects or atypical pathological pathways. Angiography visualizes intracranial circulation, not quite accessible to extracranial US (even transcranial doppler), which delivers indirect and segmental information related to cerebral circulation, which may present morphological and trajectory abnormalities. Information on the patency of intracranial collateral supply is important in the prognosis of carotid occlusion. Carotid angiography, in this case, helps to diagnose a possible subocclusive carotid stenosis, which would make the patient a candidate for a probably invasive solution [44–46, 66–71].

3. Conclusions

Patients with PAD undergoing elective vascular surgery have a high prevalence of coronary and cerebrovascular ATS with associated comorbidities (DM, renal failure, anemia) and are at an increased risk of perioperative death and MACE (MI or stroke). The management of patients with PAD refered to high-risk vascular surgical procedure for intermittent claudication, CLI or expanding abdominal aortic aneurysm requires risk stratification, optimization of medical therapies and limited use of cardiac imaging prior to surgery. Preventive coronary revascularization in patients with stable CAD, prior to the vascular operation, with the sole intention of mitigating the risk of CV complications in the perioperative period, is not effective and may be associated with significant bleeding and thrombotic risks, in particular, if stents are used. The patient, surgeon and anesthesiologist can be initially informed about the risk of surgery using modern preoperative risk indices (RCRI, NSQIP, VSG-CRI calculator). Modern biomarkers, such as BNP and high-sensitivity Tn assays, are likely to play a more substantial role in preoperative assessment in the future, but for now they are indicated for high-risk patients. A strategy of universal use of cardiac Tn in the perioperative period for active surveillance of myocardial ischemia may be more reasonable and cost-effective than the current standard of care and widespread use of cardiac imaging prior to high-risk

surgery. An elevated cardiac Tn after vascular surgery is recommended and predictive to detect perioperative ischemic events associated with a long-term mortality risk. If the cardiac biomarkers are negative and medical therapy is thought optimized, proceeding with the surgery seems safe. If the cardiac biomarkers are positive, NIST with either DSE or MPI is recommend (particular attention to whether it has potential to change management), taking into account specific patient characteristics that would afford benefit from one modality when compared to another. If the NIST is positive, then a cardiology consultation should be obtained with the appropriate preoperative steps and interventions taken to optimize the patient for their procedure. In general, preoperative coronary revascularization has a limited role, being reserved for the same indications as in routine circumstances. For the most part, chronic CV medications, such as aspirin, ACEI, ARBs and β-blockers, should be continued, but the decision should be individualized to each patient's circumstances. Ideally, thienopyridine antiplatelets therapy should be held before surgery, aside from cases of recent coronary stenting, where expert opinion should be sought. Using clinical risk assessment with biomarkers may decrease further expensive testing and might clarify, optimize risk stratification and indicate whether abnormal cardiac biomarker therapies will change outcomes [71, 72].

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Chapter 5

Risk Factors in the Patients with Extracranial Carotid Atherosclerosis

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75808

Abstract

There are vascular risk factors known to be associated with stroke. These risk factors have been shown to either directly or indirectly lead to stroke. The risk factors include hypertension (HT), diabetes mellitus (DM), smoking, hyperlipidaemia, ischemic heart disease (IHD) and atrial fibrillation (AF). Studies have shown that carotid atherosclerosis is a cause of stroke. Extracranial carotid atherosclerosis accounts for up to 40% of the ischemic strokes in the Western countries. The latest stroke guidelines recommend the routine use of Ultrasound Carotid Doppler to assess for extracranial carotid artery atherosclerotic diseases (carotid intima media thickness, plaques, carotid stenosis) in these patients. A previous study emphasized the value of carotid ultrasonography in the detection of early extracranial carotid atherosclerosis.

Keywords: extracranial, carotid, atherosclerosis, risk, factors

1. Introduction

Stroke is one of the most common diseases in the world and results in up to 10% of mortality globally [1]. Stroke is the third leading cause of mortality and long-term disability in the United States of America [2].

There are vascular risk factors known to be associated with ischemic strokes [3]. These risk factors have been shown to either directly or indirectly lead to stroke [3]. The risk factors include hypertension (HT), diabetes mellitus (DM), smoking, hyperlipidaemia, ischemic heart disease (IHD) and atrial fibrillation (AF) [3].

Studies have shown that carotid atherosclerosis is a cause of stroke [4]. Annually, about 20–30% of new strokes are due to atherosclerotic carotid artery disease [5]. The latest stroke guidelines recommend the routine use of ultrasound carotid Doppler to assess for extracranial carotid artery atherosclerotic diseases (carotid intima media thickness, plaques, carotid stenosis) in these patients [6].

Ultrasound carotid Doppler is a non-invasive and cost-effective test [7]. Carotid intima media thickness (CIMT) measurements and plaque location are evaluated on gray scale imaging (B-mode) [7]. Flow disturbance and stenosis is assessed on color Doppler [7]. The blood flow velocities are examined on spectral Doppler [7].

A previous study emphasized the value of ultrasound carotid Doppler in the detection of early extracranial carotid atherosclerosis [4]. In the world, an increased CIMT is found in 9.4% of the men and 11.7% of the women [4]. Assessment of CIMT increases with ultrasound carotid Doppler in the subjects without carotid atherosclerosis and free of previous vascular events predicts the occurrence of carotid plaque [8].

The prevalence of carotid plaque is 13.3% in the men and 13.4% in the women in the world [8]. The prevalence of extracranial carotid stenosis is 2.7% in the men and 1.5% in the women globally [8]. Stroke is associated with the plaques containing softer tissue, especially with thin fibrous cap [2].

Hyperlipidaemia is a common risk factor for extracranial atherosclerosis [9]. The risk factor of hyperlipidaemia was one of the two most common risk factors for stroke in Singapore (76.5–86.4%) [3]. Hyperlipidaemia results in an atheroma or a fibrofatty plaque leading to gradual occlusion of the arteries. As the plaques increase in size, they progressively occlude the lumen and compromise the blood flow causing stroke [10]. In the South Korean studies, extracranial atherosclerosis was associated with higher LDL levels [9, 11].

Furthermore, low levels of HDL cholesterol are associated with an increased risk of having echolucent, rupture-prone atherosclerotic plaques [12]. In addition, an increased risk of having an echolucent plaque is independently associated with increasing degree of stenosis [12]. The subjects with echolucent plaques have increased risk of ischemic cerebrovascular events and stroke independent of the degree of stenosis and cardiovascular risk factors [13].

A community-based study in Taiwan showed that hypertension strongly influenced extracranial carotid atherosclerosis and hypertension was the predictor of carotid stenosis ≥50% [14, 15]. The frequencies of hypertension among the stroke patients in the other Asian countries were: 59% in Pakistan [16], 38.3% in Japan [17], and 19–28% in China, Korea and Taiwan [17].

There are several mechanisms of stroke due to hypertension. High blood pressure results in endothelial damage, which leads to thrombi formation [18]. Hypertension is also known to accelerate the atherosclerotic process [18]. Moreover, in the general population, hypertension is a predictor of the occurrence of plaques [8]. Systolic blood pressure is significantly associated with severe extracranial carotid atherosclerosis (plaque, stenosis) [4].

The percentages of ischemic stroke patients with DM were 37% in Pakistan [16] and 30% in South Korea [11]. DM is an important risk factor for extracranial carotid atherosclerosis [14, 19]. DM affects the vascular endothelium and reduces the bioavailability of nitric oxide (NO),

which is a major anti-atherosclerotic agent [20–22]. Hyperglycemia inhibits the production of NO by restraining the activation of endothelial NO synthase [23]. In addition, the prevalence of extracranial carotid atherosclerosis is significantly higher in the ketosis-onset DM patients than in the control subjects [24]. The frequency of extracranial carotid atherosclerosis in the ketosis-onset DM patients is similar to the non-ketotic type 2 DM patients [24].

Smoking is also known to be associated with atherosclerosis of the extracranial carotid vessels [14]. The percentage of the patients with smoking history was 25% in Wasay et al.'s study [16]. Smoking leads to damage of cells that line the arteries. In addition, smoking increases the build-up of plaque constituents in the arteries. Moreover, smoking results in thickening and narrowing of the arteries [25].

Smoking history is a determinant of the occurrence of a new carotid plaque in the subjects with no previous carotid atherosclerosis and also free of previous vascular events [8]. In addition, there is a significant association between severe extracranial carotid atherosclerosis and smoking [4]. Furthermore, smoking was found to be associated with carotid plaque and extracranial carotid stenosis in several studies [9, 26, 27]. Cessation of smoking will be helpful in the management of these stroke patients.

IHD and ischemic stroke are vascular diseases [28]. IHD was present in 11.8–20% of the Singapore stroke patients [3]. Moreover, IHD was associated with carotid stenosis in a study [27]. In another study conducted in Japan on consecutive patients who had coronary angiography, 6% of them had extracranial carotid stenosis [29].

AF is known cardiovascular risk factor of stroke [30]. AF can predispose to embolism and stroke [31]. AF is commonly associated with stroke in South Asia, Western Europe, North America and Australia [32]. Increased CIMT and presence of carotid plaque are associated with increased risk of ischemic stroke in the patients with AF [33]. Higher CIMT and the presence of carotid plaque are associated with higher incidence of AF incidence [34].

Age is an important risk factor for extracranial carotid atherosclerosis, especially in the Chinese and South Koreans [9, 11, 14, 19, 35]. These patients tend to be older in age [9, 11, 19, 35]. Age is a significant predictor of the occurrence of a new carotid plaque in the general population [8]. The incremental probability of the occurrence of plaque is higher in the subject's midlife [8]. In the subjects aged ≥40 years old, the severity of carotid atherosclerosis (plaques, stenosis) was significantly associated with age [4]. Moreover, the frequency of extracranial carotid atherosclerosis significantly increases with age in the DM patients (ketosis-onset and non-ketotic DM) [24].

Male gender is also risk factor for extracranial atherosclerosis [9, 19]. 14.8% of the patients with extracranial atherosclerosis, had family history of stroke [9]. In a Chinese study, 48.4% of the healthy population with extracranial carotid atherosclerosis had obesity [19].

Elevated CIMT is associated with an increased risk of stroke [20]. Plaque rupture with subsequent embolism can lead to stroke [20]. The presence of plaque is associated with an increased risk morbidity and mortality secondary to stroke [28].

One population study showed the relationship between extracranial carotid atherosclerotic lesions with the classic risk factors such hypertension, hyperlipidaemia and smoking [28].

An European Rotterdam Elderly Study showed that hypertension, smoking and reduced serum HDL were associated with carotid artery stenosis [36]. In that study, factor VIIc and factor VIIIc (hemostatic factor) activity was higher in the patients with extracranial carotid disease [36].

Altogether, the number of classic risk factors among the patients with extracranial atherosclerosis was 1.67 in a South Korean study [11]. The number of traditional risk factors in the patients with severe extracranial atherosclerosis was almost similar (1.68) [11].

CIMT is a marker of subclinical atherosclerosis and hypertension has been known to be risk factor of atherosclerosis [28]. Therefore, proper monitoring of CIMT and treatment can potentially be helpful to these patients to prevent further progression to plaques and stenosis. In a previous study, 18.2% of the patients with extracranial atherosclerosis had history of previous stroke [11]. Among the patients with severe extracranial atherosclerosis, 21.6% of them had history of previous stroke [11].

Furthermore, a study by Amarenco et al. showed that there was a higher prevalence of coronary plaques, with concomitant carotid plaques, in patients with non-fatal ischemic stroke with no known IHD [37]. In a study done among Chinese patients, 7.8% of the patients with paroxysmal AF had a combination of extracranial carotid stenosis and IHD [30].

The miR-146a rs2910164 polymorphism may be associated with carotid vulnerable plaque risk in the Chinese patients with type 2 DM, particularly in older patients and women [38]. This polymorphism may be associated with carotid vulnerable plaque risk in the patients with DM duration of >10 years and the patients with hypertension [38].

In addition, the metabolically abnormal but normal weight subjects have increased CIMT compared to the metabolically healthy but obese subjects and metabolically healthy normal weight subjects [39]. The patients with extracranial carotid atherosclerosis are more likely to have contralateral extracranial carotid atherosclerosis [26].

In terms of ethnic variation, the South Asians have the higher prevalence of extracranial carotid atherosclerosis compared to the Europeans and Chinese [20]. The South Asians have an increased frequency of impaired glucose tolerance, hypercholesterolemia (higher total and LDL cholesterol), hypertriglyceridemia and lower HDL cholesterol [20]. In addition, the South Asians have higher concentrations of fibrinogen, homocysteine, lipoprotein (a), and plasminogen activator inhibitor-1 [20].

The Chinese have lower rates of cardiovascular disease than the Europeans [40]. Furthermore, the Chinese have a more favorable risk factor profile except for impaired glucose tolerance [40]. The Europeans are more likely to be current or former smokers [20]. The Caucasians with severe extracranial carotid stenosis are more obese than those without such stenosis, unlike the Japanese [41].

In conclusion, proper identification and optimization of the risk factors in the patients with extracranial carotid atherosclerosis in important. This will help to prevent or slow down the progression of the extracranial carotid atherosclerosis. By preventing the development of carotid stenosis, the occurrence of ischemic stroke can be minimized (**Figure 1** and **Table 1**).

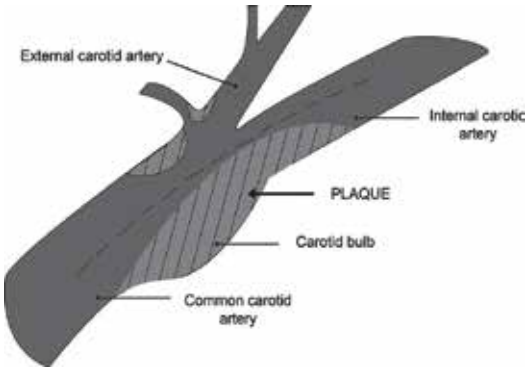

Figure 1. Diagram showing plaques at the carotid bulb extending to the internal carotid artery [2].

1. Hypertension
2. Diabetes mellitus
3. Hyperlipidaemia
4. Smoking
5. Ischemic heart disease
6. Atrial fibrillation
7. Advancing age
8. Male gender
9. miR-146a rs2910164 polymorphism
10. Metabolically abnormal but normal weight

Table 1. Risk factors of extracranial carotid atherosclerosis [9, 14, 18, 19, 28, 30, 38, 39].

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Section 3

Diagnosis of Peripheral Arterial Disease

Chapter 6

The Role of Imaging in Peripheral Arterial Disease

Stacy Willner

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75675

Abstract

Peripheral arterial disease, specifically lower limb peripheral arterial disease, can be defined as atheromatous narrowing or occlusion of an artery or arteries in the lower limb. This is becoming an ever more present disease affecting more and more people each year. Diagnosis and prompt treatment are key as the effects of untreated peripheral arterial disease can be dire. Symptoms can range from largely asymptomatic to severe pain, ulcerations, claudication, and rest pain. Treatment is dependent upon the degree of stenosis; this makes diagnosis and visualization of the affected area key. In the past, the cornerstones for diagnosis consisted of contrast, or conventional, angiography and duplex ultrasonography. Newer imaging modalities for diagnosis have since emerged, which consist of magnetic resonance angiography and, more recently, computed tomography angiography. No modality is without fault; therefore, it will be essential to consider side effects, potential risk, and specificity and sensitivity of results, all of which will be covered in this chapter.

Keywords: peripheral arterial disease (PAD), computed tomography angiography (CTA), magnetic resonance angiography (MRA), duplex ultrasonography, conventional angiography

1. Introduction

There are several instances in which non-invasive imaging can be used in patients with, or suspected of having, peripheral arterial disease (PAD). It is reasonable to consider ordering imaging for patients who are suspected to have PAD, based on risk factors, to aid in future management. Imaging can be done on a patient to confirm a diagnosis of PAD or in patients who have signs or symptoms of PAD. Most importantly, imaging will be useful in evaluating patients prior to a planned vascular intervention or to provide surveillance after a vascular intervention has been performed. This chapter will discuss the pertinent imaging modalities:

duplex ultrasonography, computed tomography angiography (CTA), magnetic resonance angiography (MRA), and the gold standard, conventional angiography. These imaging modalities will then be compared according to the latest studies.

2. Duplex ultrasonography

Duplex ultrasonography is a method that uses sound waves with frequencies above those heard by the human ear. When this ultrasound beam travels, it runs into various "targets," such as soft tissue, bone, blood, fluid, etc., and is reflected back creating an image. The term duplex ultrasonography refers to the utilization of both B-mode and pulsed Doppler analysis of the velocity of blood flowing in the various arteries and veins. B-mode, "brightness-mode," is a technology that provides real-time, gray scale images. For analyzing the presence or severity of PAD in the lower extremity, high frequency transducers are best, in that they provide excellent image resolution in superficial structures. The "Doppler shift" has been studied and described by Christian Doppler, who found that as an artery is narrowed, the blood velocity will be increased. This has served as the foundation for all vascular ultrasonography [1].

Arterial duplex ultrasonography allows direct visualization of the arteries of the lower extremities. Vessels are classified into 1 of 4 groups. The first being "normal," which is considered 1–19% stenosis, followed by 20–49%, 50–99% stenosis, and full occlusion. Knowing where and how severe various lesions are allows for the clinician to determine the best therapy, whether that be nothing at all, medical therapy, or invasive therapy, such as percutaneous transluminal angioplasty, stent, or even surgery for bypass [1]. According to Whelan et al., Doppler ultrasonography demonstrated a sensitivity and specificity of 95 and 99%, respectively, for patency versus occlusive disease, and 92 and 97%, respectively, for hemodynamically significant lesions [2].

The following are a few of the accepted clinical applications for the use of duplex ultrasonography imaging: (1) the evaluation of symptomatic patients with abnormal ABIs (<0.9) to identify lesions amenable to endovascular intervention; (2) the occlusion of occult inflow aorto-iliac disease in patients that require a lower limb femoral-distal bypass graft; (3) the evaluation of hemodynamics in distal arterial segments in patients who have an ambiguous history and/or physical exam [3].

Besides being useful for diagnosis and planning interventions, duplex ultrasonography is also useful for after an intervention has taken place [1, 3]. If a patient has received a stent or bypass, he or she will likely be closely monitored by serial ultrasonography's to make sure that the stent or bypass stays patent. Some further benefits of duplex ultrasonography are that it is non-invasive, which means that there are usually no contraindications. As far as diagnostic accuracy, studies have shown duplex ultrasonography to be similar to contrast angiography, and superior to standard MRA [3].

As was stated in the introduction, no modality is without fault, and duplex ultrasonography is no exception. First off, duplex ultrasonography requires contact with the skin. Some of the patients that need this testing done suffer from chronic leg wounds that can be severe. These wounds can preclude appropriate placement of the probe; therefore, a high-quality exam cannot be performed. Other factors that could make a high-quality exam difficult include contractures, largely edematous legs, and morbid obesity. Another thing to remember with duplex ultrasonography is that it is entirely operator dependent; it is important to have someone educated on proper technique when ordering this test. Lastly, duplex ultrasonography fails to categorize stenosis in the presence of calcified walls and/or plaques [3]. Whenever picking an imaging modality it is important to weigh the pros and cons and adjust accordingly for the specific patient.

3. Computed tomography angiography (CTA)

Another commonly utilized imaging modality is CTA. It is an attractive option for a few reasons, those being: it is non-invasive, there are shorter acquisition times, thinner slices, higher spatial resolution, and improvement of multidetector computed tomography (CT) scanners that enable scanning of the whole vascular tree in a limited period of time with a smaller (but still significant) amount of contrast medium. Some further benefits include CTA being more cost-effective than MRA, and there being less patient contraindications. Recent studies have reported a sensitivity and specificity of 98% for the diagnosis of PAD [4] (**Table 1**).

Imaging modality	Sensitivity	Specificity	Advantages	Disadvantages
Duplex ultrasonography	80–98% [2, 5]	89–99% [2, 5]	• Non-invasive • Helpful for monitoring after intervention has taken place • Low cost [3]	• Contraindications: edematous legs, morbid obesity, open sores, contractures • Operator dependent • Unable to classify calcified vessels or plaques [3]
Computed tomography angiography (CTA)	89–99% [5]	83–97% [5]	• Non-invasive • Short acquisition time • Techniques are being developed to utilize less contrast [4]	• Radiation • Iodinated contrast • Unable to classify calcified vessels [4]
Magnetic resonance angiography (MRA)	93–99.5% [5]	64–99% [5]	• Non-invasive • Iodinated contrast not needed • No radiation [5]	• Contraindications: pacemakers, other metallic implants; if patient is claustrophobic, may need sedation • Gadolinium administration and risk of nephrogenic systemic fibrosis [5]

Table 1. Summarized overview of the sensitivity, specificity, advantages, and disadvantages of the imaging modalities.

Disadvantages of CTA include exposure to radiation, which can accumulate with repeated studies and be potentially carcinogenic, along with the necessity of giving iodinated contrast, which can be problematic for those patients with kidney disease. Some patients also have allergies to iodine; a CTA can still be done, but the patient will need pre-medication with a combination of Benadryl, steroids, hydration, and possibly N-acetylcysteine, which is still under investigation. Another disadvantage includes the inability to accurately assess vessels that have been calcified [4].

4. Magnetic resonance angiography (MRA)

Gaining more popularity is the imaging modality called MRA. The most obvious benefit in using this modality to diagnose PAD is that intravenous contrast is not standardly needed, and it does not utilize ionizing radiation. Both phase-contrast (PC) and time-of-flight (TOF) MRA's are non-contrast techniques that detect blood by its movement compared with static surrounding tissue. MRA is also non-invasive, which gives it an edge over the gold standard, contrast angiography. For completeness sake, there is a form of contrast MRA that is called contrast enhanced MRA; this modality uses an intravenous contrast and relies on the T1 shortening effect of the contrast medium within the arterial system [5].

Although MRA is considered a non-invasive, cost effective, time efficient way to assess and diagnose lower extremity PAD, there are some downfalls. For example, if a patient has a pacemaker that is not compatible with magnetic resonance imaging (MRI), if he or she is claustrophobic, or have other metallic implants, MRI might be contraindicated. There is also the risk of nephrogenic systemic fibrosis with the administration of gadolinium [5].

5. Conventional angiography

Conventional angiography is the gold standard for diagnosis in PAD. This modality involves the intravascular injection of a contrast agent during planar radiographic imaging. The base images are then enhanced by background subtraction of a precontrast frame using a digital technique, such as digital subtraction angiography (DSA), which allows only the opacified arterial system to be seen on the final image. DSA is able to provide superior contrast resolution with lower doses of intravenous contrast, while also having the ability to magnify images and image vessels in real-time, which provides the option for simultaneous intervention [5].

Like the other modalities that have been discussed, conventional angiography has some downsides. In contrast to the other modalities discussed in this chapter, conventional angiography is invasive, and there can be issues with arterial punctures, such as uncontrollable bleeding or hematoma formation. It also involves higher levels of radiation, along with a strong potential for nephrotoxicity and allergic reactions to the contrast agent [5].

http://dx.doi.org/10.5772/intechopen.75675

6. Comparing the different imaging modalities

As reported above, duplex ultrasonography has a high sensitivity and specificity; however this goes down when multivessel disease is present. Normally, when compared to the "gold standard" of conventional angiography the diagnostic accuracy of duplex ultrasonography is >80% for the detection of a >50% diameter stenosis or occlusion. This diagnostic accuracy can reach up to >90% without the presence of multivessel disease. But overall, in 50% of patients with symptomatic PAD, duplex ultrasonography can detect disease amenable to endovascular therapy. Two prospective studies were done in 1990 and 2003, comparing duplex ultrasonography and conventional angiography in planning for infrainguinal bypass procedures; patient outcomes, which included limb salvage and graft patency, were similar. This indicates that, "the clinical accuracy of duplex ultrasonography to select appropriate inflow-outflow anastomotic sites for lower limb arterial bypass was equivalent to angiography" [3].

According to a systemic review that included over 100 studies that compared MRA, CTA, and duplex ultrasonography for the evaluation of lower extremity PAD, the following findings were found: contrast enhanced MRA had the highest diagnostic accuracy, with sensitivities ranging from 93 to 99.5% and specificities from 64 to 99% for the detection of whole leg arterial stenosis >50%. Two dimensional TOF MRA had sensitivities ranging from 79 to 94% and specificities from 74 to 92%. CTA appeared to be slightly inferior when compared to contrast enhanced MRA, but better than duplex ultrasonography, with sensitivities of 89–99% and specificities of 83–97%. Similar to what was stated earlier, duplex ultrasonography has sensitivities of 80–98% and specificities of 89–99%. Contrast enhanced MRA and duplex ultrasonography appeared to be more accurate for detecting proximal lesions and occlusions above the knee when compared to lesions below the knee or in the pedal artery. When comparing adverse events, MRA had the highest overall incidence of adverse events, however contrast angiography was associated with more severe adverse events. For evaluation of the whole extremity, duplex ultrasonography was the most cost-effective option when compared to CTA and MRA; however when the assessment was limited to a specific section, above or below the knee, two dimensional TOF MRA was more cost effective. Finally, when evaluating patient's attitudes and comfort levels associated with MRA, CTA, and conventional angiography it was found that, not surprisingly, conventional angiography was the most uncomfortable, followed by contrast enhanced MRA, with CTA being the most comfortable [5].

7. Conclusion

When it comes to choosing an appropriate imaging modality for a patient, it is important to consider the symptoms the patient is dealing with, whether an intervention is anticipated, and what their current situation is. PAD is a very complex disease with many available tools, imaging being one of them. Armed with the right information, a thorough history and physical exam, and an appropriate imaging modality, the patient will be on the right track to getting the help and care he or she needs.

Conflict of interest

There are no conflicts of interest.

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Section 4

Extracranial Carotid Disease

Chapter 7

Extracranial Carotid Atherosclerosis in the Patients with Transient Ischemic Attack

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75792

Abstract

Management of transient ischemic attack (TIA) is important because potentially fatal ischemic strokes can be prevented. Detection of extracranial carotid atherosclerosis in these patients is beneficial because medical therapy can be given, and in certain cases, surgery can be performed. In a Chinese study conducted on the patients with TIA, only 19% of them had extracranial carotid atherosclerosis. Another study was conducted to compare the location and the severity of atherosclerotic lesions between Americans and the Japanese who presented with carotid system TIA. This study showed that 85% of the American patients had extracranial carotid stenosis (stenosis ≥50%). However, only 16.7% of the Japanese patients had similar lesions.

Keywords: transient ischemic attack, extracranial, carotid, atherosclerosis, stroke

1. Introduction

In the patients with transient ischemic attack (TIA), ischemic strokes often occur early after the first presenting clinical features especially in the first 7 days [1–4]. Management of TIA is important because potentially fatal ischemic strokes can be prevented [5]. It is important to identify the highest risk patients urgently so that the necessary management can be instituted for appropriate early treatments [6, 7].

Neuroimaging is beneficial to stratify the risk of recurrent stroke [8]. The modalities useful for imaging of the extracranial carotid vessels are ultrasound carotid Doppler with/without

enhancement, computed tomography angiography (CTA), magnetic resonance angiography (MRA), and positron emission tomography (PET)/CT [8–14].

With improvements in vascular imaging techniques, it is now possible to risk stratify the patients on the degree of carotid artery stenosis and also on the vulnerability of the plaque to rupture [13]. The risk stratifications are based on the presence of imaging features such as intraplaque hemorrhage (IPH), plaque ulceration, plaque neovascularity, fibrous cap thickness, and presence of a lipid-rich necrotic core (LRNC) [13].

The risk of early recurrent stroke in the patients with TIA is 9.5–20% at 90 days [2, 15, 16].

The risk of early recurrent stroke is highest in patients with large artery atherosclerosis, which consists of extracranial carotid atherosclerosis and intracranial stenosis [9]. Therefore, it is important for urgent ultrasound carotid Doppler and transcranial Doppler (TCD) to be performed in these high-risk patients [9].

The carotid arteries are elastic and are predilection sites for atherosclerosis [17, 18]. Carotid intima media thickening is an indicator for subclinical atherosclerosis, and this frequently occurs earlier than atherosclerosis in coronary arteries and intracranial arteries [17, 18].

The patients who developed a hemispheric TIA due to internal carotid artery (ICA) disease had the greatest risk of ischemic stroke in the first few days after the TIA [9]. Carotid stenosis is associated with recurrent strokes [9, 19]. In the TIA patients, carotid stenosis predicted 90-day stroke [19]. Carotid stenosis is significantly associated with stroke in the short term, and also in the long term for up to 3 years [1].

In a Chinese study conducted on the patients with TIA, only 19% of them had extracranial carotid atherosclerosis [20]. Another study was conducted to compare the location and the severity of atherosclerotic lesions between Americans and the Japanese who presented with carotid system TIA [21]. This study showed that 85% of the American patients had extracranial carotid stenosis (stenosis ≥50%) [21]. However, only 16.7% of the Japanese patients had similar lesions [21]. In another study, the African-Americans had slightly more extracranial carotid atherosclerosis compared to the Caucasians [22].

In a multicenter study on the patients with TIA or minor stroke, 15.5% of the patients (28 out of 85) had at least one stenosis of ≥50% or occlusion [23]. In a recent study, 6.3% of the TIA patients had extracranial carotid artery disease [5]. In that study, 10 (35.7%) patients had moderate stenosis (50–69% stenosis), 8 (28.6%) patients had severe stenosis (70–99% stenosis), and 10 (35.7%) had total occlusion [4]. Five (17.9%) patients had recurrent TIAs before admission [5]. No patient had ischemic stroke within 90 days of TIA onset [5].

In another prospective study on the patients with TIA and minor stroke, extracranial carotid artery occlusion or stenosis ≥50% was found in 9.4% of the patients [8]. In a Japanese study, 21.8% of patients had carotid stenosis [1]. In a study conducted in Ireland, 23.8% of the TIA patients had unilateral carotid stenosis (40.4%, with 50–69% stenosis, 59.6% with ≥70% stenosis or occlusion) [19].

In the study by Coutts et al., 19% of the patients with TIA and minor stroke who developed recurrent stroke had extracranial carotid stenosis ≥50% or occlusion [8]. In comparison, only 9% of the patients with TIA and minor stroke who developed recurrent stroke had similar lesions [8].

A TIA event within 7 days before TIA (dual TIA) is a useful predictive factor for short- and long-term stroke [1]. In addition, ischemic stroke risk is elevated with increasing severity of carotid stenosis [19]. The risk of stroke is 5.4% with <50% carotid stenosis and 17.2% with severe carotid stenosis and occlusion at 90 days after TIA [19].

2. Diagnostic modalities

The advantages and disadvantages of the various imaging modalities are illustrated in **Table 1**. Ultrasound carotid Doppler is easily available, cheap, and noninvasive [19]. The sensitivity in carotid stenosis >70% is 91–95% [11, 24]. The specificity in severe stenosis of more than 70% is 86–97% [11, 24]. Being operator dependent is one of the limitations of ultrasound carotid Doppler [11]. The peak systolic velocity (PSV) analysis on the insonated tortuous vessel is difficult, and the stenosis in internal carotid artery (ICA) at the distal end also is difficult to be examined [11].

The diagnostic criteria for stenosis according to The Society of Radiologists in Ultrasound Consensus Criteria for Carotid Stenosis are used to classify the degrees of stenosis [25]. Carotid stenosis of at least 50% is defined as peak systolic velocity (PSV) ≥ 125 and end-diastolic velocity (EDV) ≥ 40. Carotid stenosis of at least ≥70% is defined as peak systolic velocity (PSV) ≥ 230 and end-diastolic velocity (EDV) ≥ 100 [25].

Contrast-enhanced ultrasound is a novel, noninvasive, and cost-effective technique to assess plaque morphology and characteristics [13, 14]. Contrast-enhanced ultrasound assists with the identification of several surrogate markers of vulnerable carotid plaques [14]. The use of ultrasound microbubbles allows a reliable detection of microulcerations [14]. As microbubbles are intravascular tracers, the detection of individual microbubbles inside the plaque signifies intraplaque neovessels [14]. The limitation is the poor sensitivity and specificity for detection of lipid-rich necrotic core and plaque hemorrhage compared with MRI [13].

An early evaluation of the extracranial vessels with computed tomography (CT) and CT angiography (CTA) predicts recurrent stroke and functional outcome in the patients with TIA [8]. In many hospitals especially in the developing countries, CTA is more readily available than magnetic resonance imaging (MRI) due to the cost factor [8]. The doctors will utilize the modality which is more easily and rapidly available in the hospitals [8].

Multislice helical CT scan machines with CTA are widely available in many hospitals [8]. CTA involves the administration of intravenous contrast media to evaluate the extracranial and intracranial vessels with high spatial resolution [8, 26].

Multirow spiral CTA helps with the evaluation of plaques and stenosis [11, 27, 28]. CTA helps to identify large artery atherosclerosis [10, 29]. CT also enables high-resolution imaging and accurately detects ulceration and calcification [13]. The limitation of CTA is the inadequate detection of the morphology of the plaque and its content [11, 27, 28]. In addition, CT is unable to distinguish between lipid-rich necrotic core and intraplaque hemorrhage accurately [13].

There is a technological advancement in the imaging of extracranial carotid atherosclerotic lesions with high-resolution MRI and MRA [11]. Presently, MRI is the gold standard in the

imaging of carotid plaque [13]. MRI has high resolution and high sensitivity for assessment of intraplaque hemorrhage, ulcerated plaque, and lipid-rich necrotic core [30]. The limitation of MRI is time factor [13].

Careful examination of these lesions with high-resolution bright-blood and black-blood MRI analysis of the extracranial carotid vessels accurately evaluates the contents in the plaques [11]. This is performed using the 3.0-Tesla MRI machine [11, 31, 32]. The advantage is the high spatial resolution [11, 31, 32].

The time-of-flight sequence bright-blood technique demonstrates calcified plaques [11, 33]. Black-blood technique is the MRI technique in which the imaging of vessel wall adjacent to the intravascular space is clearer [11, 33]. The bright-blood and black-blood techniques are highly correlated with the diagnosis of contrast-enhanced MRA in the degree of stenosis [11]. The sensitivity and specificity of using MRI technique to detect stenosis of ≥50% are 88.9 and 100%, respectively [11]. The accuracy of MRI diagnosis of similar degree of stenosis is 97.9% [11].

The fibrous cap is isointense in T1-weighted image (T1WI) and hyperintense in proton density weighted image (PDWI) and T2-weighted image (T2WI) [11]. The lipid core is isointense or hyperintense (mild) in T1WI [11]. It is isointense, hyperintense, or hypointense in PDWI and hypointense in T2WI [11].

Ulcerative plaques are characterized by irregular intravascular space surface in the black-blood sequences [11]. In addition, the black hypointensity band is not observed in three-dimensional time-of-flight MRA [11]. The hypointensity band is not continuous, and the intrusion of hyperintensities into the plaques can be picked up [11].

In a recent study on extracranial carotid atherosclerosis with MRI, visual and quantitative analyses demonstrated that the border between the plaque and vessel lumen was better delineated on three-dimensional (3-D) T1-weighted turbo-spin echo black-blood (TSEBB) MRI than on 3-D T1-turbo field-echo black-blood (TFEBB) MRI [12]. Three-dimensional T1-TSEBB MRI was superior to 3-D T1-TFEBB MRI for delineating carotid plaques [12]. But the high signal plaques were underestimated on 3-D T1-TSEBB MRI [12]. In another recently conducted study, 7.0-Tesla MRI enables adequate evaluation to determine luminal and vessel wall areas [34]. Signal hyperintensity in 7.0-Tesla MRI images was inversely proportional to calcification [34].

Positron emission tomography (PET)/CT is an effective modality to evaluate active inflammation in the plaque [13]. However, PET/CT does not allow for assessment of anatomy, ulceration, intraplaque hemorrhage, and lipid-rich necrotic core [13]. In addition, a combination of [18] F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and MRI are complementary to predict high-risk carotid plaque, such as lipid-rich or hemorrhagic plaque [35]. FDG-PET accurately evaluates the lipid-rich and inflamed plaque [35]. MRI is valuable to identify unstable plaque with a large intraplaque hemorrhage [35].

Digital subtraction angiography (DSA) was the gold standard for the assessment of intracranial and extracranial vasculature before the era for MRI [11, 36]. This investigation method

has numerous limitations [11, 36]. Firstly, DSA is invasive [11, 36]. Secondly, the sensitivity is only 46% and the specificity is 74% [11, 36].

Higher levels of cystatin C are independently associated with symptomatic extracranial internal carotid artery (ICA) stenosis, in patients with noncardioembolic stroke [37]. Cystatin C is a biomarker and it is a protein with low molecular weight of 13 kDa [38]. Cystatin C is a cysteine proteinase inhibitor [38].

Cystatin C is an independent risk factor for cardiovascular events and all-cause death in the elderly patients with a normal estimated glomerular filtration rate (eGFR) [39, 40]. It has been suggested that cystatin C levels are associated with inflammation and atherosclerosis [41].

The association between cystatin C and the risk of cardiovascular events is observed in the patients with asymptomatic carotid atherosclerosis, thus ultrasound carotid Doppler can be ordered to detect the carotid abnormalities early [38] (**Table 1**).

	Advantages	**Disadvantages**
Conventional ultrasound carotid Doppler [11, 24]	• Easily available • Cheap • Noninvasive	• Operator dependent
Contrast-enhanced ultrasound [13, 14]	• Noninvasive • Cost-effective • Detection of microulcerations	• Poor sensitivity and specificity for detection of lipid-rich necrotic core and plaque hemorrhage
CT/CTA brain and carotid [8, 13, 26–28]	• More easily and rapidly available in the hospitals due to lower cost • High spatial resolution	• Administration of contrast media, therefore can cause allergy • Inadequate detection of the morphology of the plaque and the content • Cannot distinguish between lipid-rich necrotic core and intraplaque hemorrhage accurately
MRI/MRA brain and carotid [11, 13, 30]	• Gold standard in the imaging of carotid plaque • High resolution and high sensitivity to assess intraplaque hemorrhage, ulcerated plaque, and lipid-rich necrotic core	• Time factor • Cost factor
PET/CT [13, 18, 35]	• Evaluates active inflammation in the plaque	• Not good in the assessment of anatomy, ulceration, intraplaque hemorrhage, and lipid-rich necrotic core
Digital subtraction angiography [11, 36]	• Very accurate	• Invasive • Poor sensitivity • Poor specificity

Table 1. Advantages and disadvantages of the various imaging modalities.

3. Therapeutic options

Detection of extracranial carotid atherosclerosis in these patients is beneficial because proper management can be given [32, 42]. The patients with TIA due to extracranial carotid stenosis should be given intensive medical therapy [42]. Intensive medical therapy consists of pharmacological management and lifestyle interventions [42].

The pharmacological management involves antiplatelet therapy and statin use [5, 42]. The antiplatelet therapy which routinely administered is aspirin or clopidogrel [43]. Adequate blood pressure control is necessary with a target blood pressure of less than 140/90 [42]. A reduction in blood pressure to the ideal level slows down the progression of carotid artery stenosis and also reduces the carotid intima media thickness (CIMT) [43]. Identification and treatment of vascular risk factors are important [43].

Lifestyle changes involve Mediterranean-style diet, exercise, and smoking cessation [42, 43]. In addition, lifestyle choices such as unhealthy diet and excessive alcohol intake are modifiable risk factors [43]. The combination of dietary modification, physical exercise, and use of aspirin, statin, and an antihypertensive agent can give a cumulative relative stroke risk reduction of 80% [43]. The antiplatelet therapy and statin use reduce the risk of recurrent stroke in patients with symptomatic extracranial carotid stenosis [5].

4. Carotid endarterectomy and carotid artery stenting

In the patients with carotid stenosis of 70–99%, the revascularization procedures such as carotid endarterectomy (CEA) and carotid artery stenting (CAS) may be considered [5, 42]. The patient with a low-grade stenosis but an ulcerated plaque or intraplaque hemorrhage may benefit more from a revascularization procedure than a patient with a stable 70% asymptomatic stenosis with a thick fibrous cap [13].

5. Carotid endarterectomy and carotid artery stenting in symptomatic extracranial carotid stenosis

Carotid endarterectomy and carotid artery stenting reduce the risk of recurrent stroke in patients with symptomatic extracranial carotid stenosis [5]. The revascularization procedures reduce the 90-day risk of subsequent ischemic stroke in the patients with severe extracranial carotid artery stenosis [5]. While awaiting the revascularization procedures, a combination of aspirin and clopidogrel in recently symptomatic patients with carotid stenosis can be given [43].

MR plaque imaging is useful in identifying revascularization candidates who are better candidates for carotid endarterectomy than carotid artery stenting [13]. This is because high

intraplaque signal on time-of-flight imaging is associated with vulnerable plaque and in-creased rates of adverse events in patients undergoing stenting but not carotid endarterectomy [13].

In the recent guidelines, carotid endarterectomy is likely the preferred option for the management of asymptomatic carotid stenosis [44, 45]. Carotid artery stenting has higher risk of periprocedural stroke and mortality [44–46]. Carotid endarterectomy is safer in comparison to carotid artery stenting [44, 45]. The risk of periprocedural stroke and mortality after carotid endarterectomy has declined tremendously throughout the years [47].

However, carotid endarterectomy is associated with an increased risk of periprocedural myocardial infarction [44, 45, 48]. To date, the long-term outcomes of these two modalities remain uncertain [44]. In patients with high risk of periprocedural complications, best medical treatment is recommended by the American Heart Association and the Society for Vascular Surgery [32, 44, 49].

6. Conclusion

In conclusion, evaluation of extracranial carotid atherosclerosis in the patients with TIA is very important. There are several modalities which can be employed to investigate for extracranial carotid stenosis. Pharmacological and nonpharmacological management can be given to the patients with extracranial carotid atherosclerosis.

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Section 5

Genetics in Peripheral Arterial Disease

Chapter 8

Genetics in Peripheral Artery Disease

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.77209

Abstract

Besides traditional risk factor, it has been proved that genetics and gene–environment interaction have a possible independent role in the development and progression of peripheral arterial disease (PAD). Knowledge about such genetic factors will increases our understanding about pathophysiologic mechanisms of PAD and could facilitate the therapeutic approaches. Human genetics has gone through an advanced improvement and it increases our chance to acquire better diagnostic and therapeutic approaches. In this chapter, we try to provide an update on the genetics of PAD, which is mostly about genome-wide association studies, linkage analyses, heritability, candidate gene studies, and epigenetics. Finally, we discuss challenges and future developments of researches in PAD genetics.

Keywords: peripheral arterial disease, genetics, genome-wide association study, linkage analyses, heritability, candidate gene studies, epigenetics

1. Introduction

Common cause of PAD is atherosclerosis. Besides environmental risk factors (e.g., smoking, gender, age), some heritable risk factors are described for atherosclerosis. These are included hyperlipidemia, hypertension and diabetes mellitus. A reliable genetic marker could identify those individuals with PAD and accelerate their treatment. Besides, finding new genetic targets uncover new insights to the pathophysiology of PAD, and consequently new target for the cure. Earlier studies suggested heritability of PAD [1–4]. One study on monozygotic and dizygotic pairs revealed that with the similar environmental risk factors 48% variability of Ankle brachial Index (ABI) could be explained by additive genetic effects [2]. GENOA study

(Genetic Epidemiology Network of Arteriopathy) and the Framingham Offspring cohort study also found heritability in ABI variations [3, 4]. The degree of genetic variations on the PAD, regardless of the influences of other risk factors, remains to be revealed.

2. Genetic studies

Table 1 demonstrates comparisons between different genetic tests.

2.1. Linkage analysis

Genetic linkage analysis has the power to identify parts of genome that contain genes that could be inherited together. In this kind of genetic study, low resolution genome scanning investigates for genetic markers (microsatellites and Single nucleotide polymorphisms-SNPs) and that are pass to the next generation with the phenotype of interest. The results express in logarithm of the odds (LOD). Positive LOD indicates that co-segregation of two genetic markers is more likely, and negative LOD favors that likelihood less likely. It is advisable to consider LOD more than three statistically significant [5]. Next step is then to map neighboring region of the genome with tied association between genetic marker and phenotype.

Three studies demonstrated relation between different loci and PAD [3, 6]. First Gudmundsson and colleagues [6], identified a locus as "PAOD1" on chromosome 1p31 (LOD = 3.93; $p = 1.04 \times 10^{-5}$) conferring susceptibility to PAD even after nullifying the effects of diabetes mellitus, hypertension and hyperlipidemia. Interestingly, the genes responsible for PAOD1 did not identified which is not surprising based on the difficulties for analyzing genetic background of a complex disease such as PAD. Another study demonstrated the association of ankle-brachial index (ABI) with 250 microsatellite markers on chromosomes 1p, 6q, 7q, and 10p in 1310 African Americans and on chromosomes 3p and 3q in 796 non-Hispanic whites [3]. This study was also unable to demonstrate any evidence of linkage to the PAD trait.

Genetic test type	Advantages	Disadvantages
Single gene/panel gene sequencing	Cost; no off-target incidental findings	Low sensitivity
Oligonucleotide microarray	High resolution, good copy number detection	No detection of balanced rearrangements
Genome sequencing	Full coverage of DNA sequence	Cost, turnaround time, analytical challenges, inaccurate for SNPs with lower frequency
GWAS	novel marker finding	high participants number
Linkage	studying different areas across the genome, analyzing multiple genetic markers at the same time	It needs a high participants number with several affected generations, less helpful for complex disorders

Table 1. Comparison of different genetic tests for PAD genetics analysis.

Although, linkage analysis does not require specific candidate gene and scans full genome, it did not show promising results. That could be related to lack of large family pedigrees and polygenic nature of PAD. Linkage analysis cannot identify the genetic contributions arise from many genes each with small effect sizes.

2.2. Genome-wide association study

In this observational study, a genome-wide set of genetic variants (SNPs) can be screened in a large cohorts of patients. This approach determines the associations between SNPs and specific phenotype compared to control individuals. Unlike linkage analysis, GWAS has the ability to detect modest genotypic effects.

In one study rs10757278 SNP at 9p21 was found to be associated with PAD (OR = 1.14, $p = 6.1 \times 10^{-5}$), but exclusion of known CAD cases from sample sets reduced the effect of this variant significantly (OR = 1.09, p = 0.075) [7]. Another similar study showed an association between 9p21 SNP (rs 1,333,049) with severity and prevalence of PAD [8]. A Japanese study on 785 PAD and 20,134 control individuals found rs9584669 in IPO5/RAP2A related protein 2A (OR = 0.58, $p = 6.78 \times 10^{-14}$), rs6842241 in endothelin receptor type A (ENDRA gene; $p = 5.32 \times 10^{-9}$), and rs2074633 in histone deacylase 9 (HDAC9 gene; $p = 8.43 \times 10^{-8}$) loci with susceptibility to PAD [9]. Thorgeirsson et al. identified a common variant (rs1051730) in the nicotinic acetylcholine receptor gene cluster on chromosome 15q24 with higher risk for PAD (OR = 1.19, $P = 1.4 \times 10^{-7}$) [10]. A GWAS study found rs7025486 at 9q33 associated with PAD (OR = 1.14, $p = 3.9 \times 10^{-5}$) [11]. An investigation performed on 699 PAD and 1540 Japanese controls identified rs1902341-A to have a strong association with PAD (OR = 1.31, $p = 4.7 \times 10^{-7}$) [12]. A recent meta-analysis with a total of 41,692 participants of European ancestry demonstrated that rs10757269 at 9p21 had the strongest association with ABI and achieved genome-wide significance ($p = 2.46 \times 10^{-8}$) [13].

After above mentioned meta-analysis, one study investigated 537,872 SNPs in 1641 PAD and 1604 control individuals in The Electronic Medical Records and Genomics consortium (eMERGE)-based GWAS of PAD [14]. They revealed that rs653178 in the ATXN2-SH2B3 locus was significantly associated with PAD (OR = 1.22, $p = 6.46 \times 10^{-7}$). Another outcome of this study was that neither loci was linked to PAD after investigation of prior known SNPs related to PAD. eMERGE analyses of PAD GEWAS results could not reveal any strong associations between SNPs and PAD by investigating of mitochondrial SNPs and haplogroups in 1652 PAD and 1629 control individuals [15].

2.3. Candidate gene studies

This kind of study focuses on differences in allele frequency of a known specific variant between cases and controls among unrelated individuals. With ability for finer mapping of the causal variant, association studies demonstrate greater power to detect modest genetic effects. Generally, search of insertions, deletions, and individual SNPs among cases and controls points out to genes to be associated with the development of atherosclerosis and changes

in various vascular biology pathways such as lipid metabolism [16], hemostasis [17–21], homocysteine [22–24], inflammation [25, 26], angiotensin converting enzyme [27], leukocyte adhesion [28], platelet activation and aggregation [29, 30], endothelial function [31, 32], and smooth muscle cell migration. A recent meta-analysis of around 50,000 SNPs and across about 2100 genes found only three SNPs associated with ABI or PAD [33]. They demonstrated that rs2171209 in SYTL3 ($p = 6.02 \times 10^{-7}$) (originally linked to lipoprotein (a)) and rs290481 in TCF7L2 ($p = 7.01 \times 10^{-7}$) (linked to diabetes mellitus type 2) were significantly associated with ABI and CYP2B6 ($p = 4.99 \times 10^{-5}$) (linked to smoking behavior) was associated to PAD.

2.4. Epigenetics

By definition, epigenetics is a science of long-lived or even hereditary modification of gene function without alteration of DNA sequence. In epigenetics, DNA could go through methylation, histone post-translational modifications, or microRNAs (miRNA), long non-coding RNA (lncRNA) mechanisms [34, 35]. miRNAs are small (≈22 nucleotides) single-stranded RNAs that inhibit translation of mRNA after binding to a target gene. Each miRNA can regulate several genes, because they do not require 100% base pair match. lncRNAs defined as more than 200 nucleotide long transcripts with function other than translation to protein.

Epigenetic changes have been described in association with some PAD risk factors [36, 37]. Hyperhomocysteinemia induces DNA methylation and could contribute to development and progression of PAD [36]. DNA hypomethylation caused by smoking has been reported [37].

Most of the epigenetic studies relevant to PAD are currently about miRNAs. There are two approaches to explore the role of miRNA in PAD. They have involved either a small number of candidate intracellular miRNA which are known for their role in vascular diseases or the measure of a large cluster of miRNAs by microarrays. A miRNA SYBR Green Real-Time PCR assessed the alteration of miR-130a, miR-27b and miR-210 expression in PAD [38]. A whole-genome miRNA transcriptome profiling revealed downregulation of 12 miRNAs in PAD compared to controls [39]. Later, the same research group detected significant downregulation of miR-15a, miR-196b, and let-7e and upregulation of miR-411 in 40 PAD and 40 control individuals [40].

Alterations in mitochondrial DNA (mtDNA) were proposed as a pathway for myopathy in PAD [41]. Mitochondrial dysfunction could be as a result of bouts of ischemia in these patients which causes damage to mitochondrion (mitochodriopathy).

2.5. Whole genome/exome sequencing

While massively parallel sequencing has not been performed on PAD patients specifically, some results from researches on atherosclerosis could be attributed to PAD. In one study, exonic regions of two persons with the early atherosclerosis were sequenced with next generation sequencing platform, and they revealed a rare missense mutation (Ser818Cys) in

INO80D, a subunit of the human INO80 chromatin remodeling complex [42]. INO80 complex is involved in cardiovascular physiology and development [43]. Another study repeated this result in two patients with aortic hypoplasia, diffuse atherosclerosis, and PAD.

2.6. Mendelian randomization

This epidemiologic study design incorporates genetic results into epidemiologic methods. Mendelian randomization studies offer evidence for causal relations between risk factors and disease outcome.

Mendelian randomization has been used to examine the relations between polymorphisms of specific genes and the prevalence of coronary heart disease or myocardial infarction [44]. Recently, it is demonstrated that each standard deviation (SD, 2.76 points) increase in body mass index (BMI)-composite genetic risk score was associated with 0.43 in BMI and an odds ratio for PAD of 1.17 [45].

3. Discussion

As multiple atherogenic pathways are involved in the pathophysiology of PAD, a profound monogenic effect is unlikely [46]. Environmental influences such as age, smoking, sport, ethnicity, and diabetes mellitus status besides genetic effects could vary the outcome for this disease. GWAS results are not comprehensive. It could be due to modest effect of susceptible variants. To power GWAS analysis, large sample sizes are needed. GWAS results so far revealed limited results. Two linkage studies did not demonstrate breakthrough to identify significant mechanisms behind inheritance of PAD. SNPs association studies have provided weak and/or conflicting findings results. Next generation sequencing and epigenetics seem to provide some promising future. Whole-genome or exome sequencing or NGS-based RNA-sequencing has identified new causative links between new genes and PAD. It is imperative to merge deep sequencing data of the DNA findings with epigenetic data to find more interesting results. This is challenging as these methods produce huge amount of data to analyze. Environmental-Wide Association Study demonstrates gene-by-environment interactions. This new method to study inter-relation between environment and genomics was a topic in ascertaining causality in type II diabetes mellitus [47]. They showed that the pesticide heptachlor epoxide was associated with type II diabetes mellitus. This new method has some places in gene-environment studies in PAD.

In the future, we may apply personalized medicine on the basis of genetic analysis and treat the patient by specific therapeutic agents.

Conflict of interest

All authors declare no conflict of interest.

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Edited by Nishtha Sareen and Abhishek Ojha

"Peripheral Arterial Disease - A Practical Approach" is an honest effort to provide a clinically relevant approach to the management plan in patients presenting with peripheral vascular symptoms. We have summarized the most pertinent practical aspects of peripheral vascular disease, their clinical implications, diagnostic testing, therapeutic interventions and innovations. We hope this book serves as a reference for basic and advanced peripheral vascular care.

Published in London, UK

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ISBN 978-1-83881-684-1