C. Lamina[1]
C. Meisinger[1]
I. M. Heid[1]
B. Rantner[2]
A. Döring[1]
H. Löwel[1]
H. E. Wichmann[1]
F. Kronenberg[1, 2]

Ankle-Brachial Index and Peripheral Arterial Disease

Knöchel-Arm-Index und periphere arterielle Verschlusskrankheit

Zusammenfassung

Patienten mit peripherer Arteriosklerose und insbesondere solche mit Claudicatio intermittens haben ein deutlich erhöhtes Risiko für kardio- und zerebrovaskuläre Morbidität und Mortalität. Das Schicksal dieser Patienten wird weniger durch lokale Komplikationen im Bein als durch systemische Komplikationen im Bereich der koronaren und der zerebralen Gefäße geprägt. Durch Untersuchungen in der KORA-Studie 2004/2005 (F3), einer Nachuntersuchung der Teilnehmer der MONICA-Studie 1994/1995 (S3), werden wir versuchen, biochemische sowie genetische Risikofaktoren für die periphere arterielle Verschlusskrankheit zu identifizieren. Einer der uns besonders interessierenden Kandidaten ist das antiatherogene Apolipoprotein A-IV.

Schlüsselwörter
Periphere Atherosklerose · Claudicatio intermittens · KORA · Genetik · Apolipoprotein A-IV

Abstract

Patients with peripheral arterial disease including those with intermittent claudication have a high risk for cardiovascular and cerebrovascular morbidity and mortality. The outcome of patients with intermittent claudication is less limited by local complications in the leg than by the systemic complications of coronary and cerebral vessels. About 30% of these patients will die within 5 years, three-quarters of them due to vascular events. Analyses using data of the KORA Study 2004/2005 (F3), a follow-up examination of the participants of the MONICA Survey 1994/95 (S3), will try to identify biochemical as well as genetic risk factors for peripheral arterial disease. The anti-atherogenic apolipoprotein A-IV will be one of our candidates of interest.

Key words
Peripheral arterial disease · intermittent claudication · KORA · genetics · apolipoprotein A-IV

Definition of peripheral arterial disease

Peripheral arterial disease (PAD) is caused by an occlusive disorder of the lower limb arteries. In most of the cases it is caused by atherosclerotic and atherothrombotic processes. Peripheral arterial disease can be asymptomatic or symptomatic. In clinical terms, PAD is divided into Fontaine's four stages (see Table **1**) [1]. Stage II is called intermittent claudication and more advanced stages (III and IV) are considered as lower limb ischemia [1].

Diagnosis of PAD

For epidemiologic purposes, the most useful noninvasive test is the ankle-brachial index (ABI) measured by using a hand-held Doppler probe (for explanation see Fig. **1**). The ABI correlates closely with direct intraarterial recordings [2, 3]. In the at present ongoing KORA Study 2004/2005 (F3) we are using this very inexpensive, rapid and painless method that can be well standardized and which shows a marginal interobserver variability

affiliation
[1] GSF National Research Center for Environment and Health, Institute of Epidemiology, Neuherberg, Germany
[2] Innsbruck Medical University, Department of Medical Genetics, Molecular and Clinical Pharmacology, Division of Genetic Epidemiology, Innsbruck, Austria

correspondence
Florian Kronenberg, MD · Innsbruck Medical University, Department of Medical Genetics, Molecular and Clinical Pharmacology, Division of Genetic Epidemiology · Schöpfstraße 41 · 6020 Innsbruck · Austria

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Table **1** Classification of peripheral arterial disease according to Fontaine [1]

stage I:	asymptomatic arteriopathy
stage II:	exercise-induced ischemia
stage IIa:	intermittent claudication, pain during walking, relief of symptoms when standing, compensated disease: walking distance > 200 m
stage IIb:	decompensated disease: walking distance < 200 m
stage III:	ischemic rest pain
stage IV:	trophic ulcers and/or gangrene

[4, 5]. A resting ABI of 0.90 is up to 95% sensitive in detecting angiogram-positive disease (ABI ≤ 0.90) and almost 100% specific in identifying asymptomatic individuals (ABI > 0.90) [6, 7]. However, the ABI may be inaccurate if the artery is not compressible in case of a sclerosis of the arterial media, as it occurs often in patients with diabetes mellitus or patients with kidney diseases [1].

Besides the ABI, the Rose questionnaire or the Edinburgh Claudication questionnaire [8] (an improved version of the Rose questionnaire), can be very helpful in epidemiological studies to identify symptomatic PAD. The Edinburgh Claudication questionnaire is used in F3.

Additional optional diagnostic procedures are a duplex sonography, an oscillographic examination, magnetic resonance imaging, computed tomography, digital substraction angiography and pulse detection which are suitable for the localization of the occluding process. In the clinical setting, the combination of duplex sonography, ABI, oscillography and pulse detection has a very high accuracy even in diabetic patients. The walking distance is determined by constant load treadmill test (speed 3.2 km/h and a grade of 12%) for classification of Fontaine stadium IIa and IIb and is besides the ABI a suitable parameter for studying the progression of PAD.

Epidemiology of PAD

Epidemiological studies show that the prevalence of intermittent claudication (stage II of Fontaine) is 3% to 6% around the age of 60 years [1]. Women show a lower prevalence than men. Detailed analysis of the available data suggests that for every patient with intermittent claudication there are probably another three with asymptomatic disease causing a 50% or greater stenosis of the arteries supplying the legs [1, 9]. This asymptomatic disease despite major stenosis and even occlusions of vessels is explained by sufficient blood supply by collateral arterial vessels. The high rate of asymptomatic disease is in accordance with a recent cross-sectional study from Germany in 6880 primary care patients aged 65 years and older which showed a prevalence of PAD of 19.8% and 16.8% for men and women, diagnosed by an ankle-brachial index (ABI) < 0.9 [10]. An ABI below 0.9 detects even asymptomatic disease (Fontaine stage I). This major differences in the prevalence of asymptomatic and symptomatic PAD is supported by the Rotterdam Study which reported a prevalence of asymptomatic PAD determined by an ABI < 0.9 in 19.1% of the population aged 55 years and older. Symptoms of intermittent claudication, however, were only reported in 1.6% of the study population [11].

Besides age and sex, risk factors for intermittent claudication are diabetes mellitus, smoking and hypertension with odds ratios of approximately 2 to 3. Conflicting evidence exists regarding the relationship between hyperlipidemia, fibrinogen, homocysteine, hypercoaguability, family history and PAD [1]. Up to now, few population-based data on incidence and prevalence of PAD and their determinants are available.

PAD and risk for cardiovascular and cerebrovascular disease

Most studies on the prevalence of coronary artery disease (CAD) in patients with PAD were based on patients with intermittent claudication and show that history, clinical examination, and

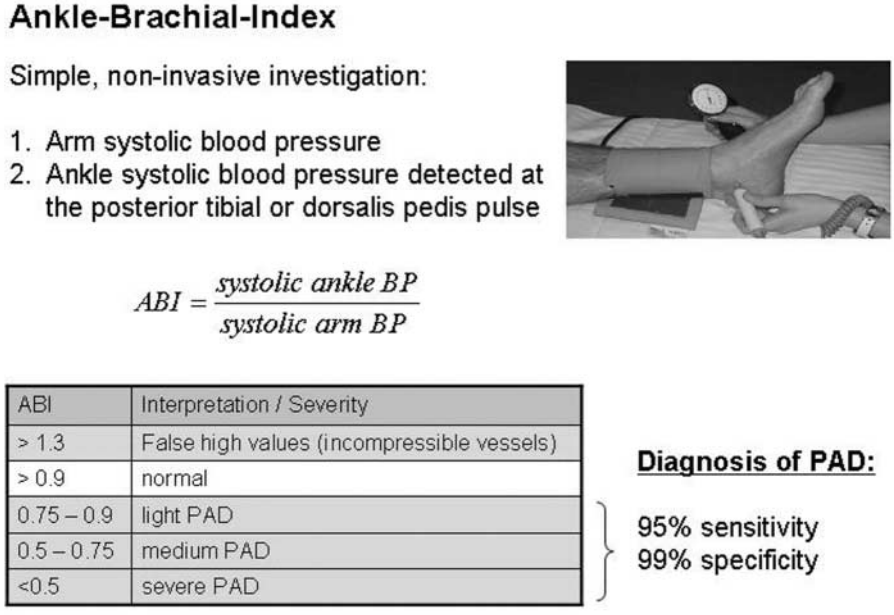

Fig. **1** Use of the Ankle-Brachial Index (ABI) to diagnose peripheral arterial disease (PAD). To correctly perform the ABI, the investigated person has to be recumbent for 5 minutes. Then the systolic blood pressure in both arms is measured and the higher value is used for the brachial portion of the index. The systolic blood pressure in the ankles is then measured using the dorsalis pedis and posterior tibial arteries. The blood pressure cuff is just placed above the ankle and a Doppler is used for ascertaining the systolic blood pressure. As with the brachial portion, the higher ankle systolic pressure value is used for calculation. Finally, the ABI is calculated by dividing the ankle by the brachial systolic blood pressure.

electrocardiography typically indicate the presence of CAD in 40% to 60% of such patients (Fig. **2**) [12 – 15]. The relationship between PAD and cerebrovascular disease (CVD) is less pronounced: Aronow and Ahn observed that 33% of patients with CVD also had PAD [16]. A major problem arises by the fact that CAD might be asymptomatic, undetected and untreated for a prolonged time if exercise of the patients is severely limited by claudication. This often results in fatal CAD events especially in this half of the patients who have symptomatic intermittent claudication and will nevertheless not consult a medical doctor [13].

The fate of patients with intermittent claudication is less limited by the local outcome in the leg than by the systemic outcome of coronary and cerebrovascular vessels (Fig. **2**). About 75% of the patients show stable or improving intermittent claudication over 5 years by strict risk factor management (e. g. smoking cessation, adequate antihypertensive, lipid-lowering and antidiabetic treatment, exercise training). Further 25% of the patients will deteriorate including those 5% who will require an intervention and 2% who will need a major amputation. Only 50% to 60% of all patients will be alive after 5 years without suffering a new cardiovascular event. Non-fatal cardiovascular events will occur in 5% to 10% of the patients. About 30% of the patients will die within 5 years, three quarters of them due to vascular events (mainly of cardiac and cerebral origin) (Fig. **2**) [11, 17 – 19]. Many studies showed that the 5-, 10-, and 15-year mortality rates from all causes are approximately 30%, 50%, and 70%, respectively – a prognosis that is not better than that following resection of a Duke's B carcinoma of the colon (i. e. a colorectal cancer that has spread through the wall of bowel) [1, 20].

Taken together, there is clear evidence that the real danger for the patients with symptoms of leg ischemia and intermittent claudication is not the extremity loss but premature cardiovascular complications or death. Therapeutic priority should therefore be focused on the systemic rather than the local outcome. According to the definition of critical issues of the TransAtlantic Inter-Society Consensus (TASC) Working Group major diagnostic efforts should be made to identify those PAD patients who have the highest risk for cardiovascular events [1, 21]. This is even more mandatory since it is not possible to use e. g. coronary angiography as a general screening tool with short screening intervals (e. g. yearly) in all PAD patients. It might be a better approach to invasively screen only those patients who are exposed to particular risk factors. All together, population-representative studies should be used, to identify the PAD risk of the general population with special regard to preventive strategies.

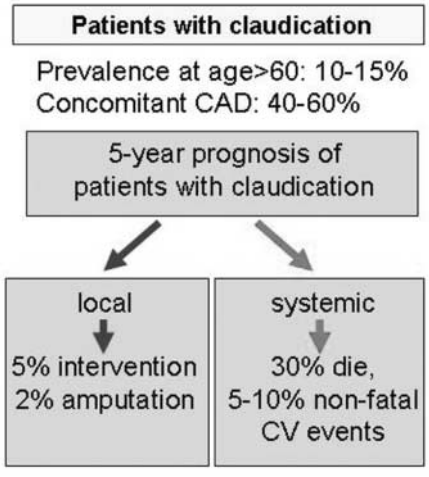

Fig. **2** Prevalence and 5-year fate of patients with intermittent claudication (according to reference [1]).

PAD in F3

Since risk factors for PAD are not yet fully identified, we will investigate biochemical as well as genetic candidates and their value for risk assessment in men and women from the general population. We will prove the independence of these parameters from the already known risk factors (e. g. smoking, diabetes mellitus). Therefore, the ABI is measured in the participants of F3. Additionally, the Edinburgh questionnaire is used to distinguish symptomatic PAD. In a first step, data analysis will be performed in terms of a cross-sectional study. However, the obtained measures might be useful for future studies in the cohort.

Apolipoprotein A-IV as an example for biochemical parameters

Human apolipoprotein A-IV (apoA-IV) is a 46 kDa glycoprotein [22] with mean plasma concentrations of about 15 mg/dL. The general physiological function of apoA-IV is not clear. Numerous in vitro studies suggest apoA-IV to participate in several steps of the reverse cholesterol transport pathway, which removes cholesterol from peripheral cells and transports it to the liver and steroidogenic organs where cholesterol can be metabolized [23 – 28]. Therefore, this pathway and its collaborators are considered as key elements to protect against atherosclerotic events. Another potentially anti-atherogenic effect of apoA-IV is its endogenous antioxidative capacity described recently [29, 30]. Even an influence of apoA-IV satiety [31] and on body weight regulation has been described [32 – 34].

In vivo studies in genetically modified animals support this anti-atherogenic role for apoA-IV. Fat-fed mice that overexpress either human [35] or mouse apoA-IV [36] demonstrated a significant reduction of aortic atherosclerotic lesions compared to control mice. Atherosclerosis was even inhibited by overexpression of human apoA-IV in apoE-deficient mice, which are hyperlipidemic and develop severe atherosclerosis even on chow diet [35].

In line with data in mice overexpressing apoA–IV, we recently demonstrated for the first time that low apoA-IV plasma concentrations are associated with CAD in humans [37]. Plasma apoA-IV levels were significantly lower in 114 male Caucasian subjects with angiographically defined CAD when compared to 114 age-adjusted male controls (10.2 ± 3.8 mg/dL vs. 15.1 ± 4.0 mg/dL, $p < 0.001$). Having low compared to high plasma HDL cholesterol concentrations increased the probability of being a patient with CAD about 2.3 and 2.5 times in the group with high and low apoA-IV plasma concentrations, respectively. On the other hand, having low apoA-IV concentrations increased the odds about 6-fold in both groups with high and low HDL cholesterol concentrations (Fig. **3**). Very similar odds ratios were observed for apoA-IV and triglyceride concentrations. This clearly shows that the association of apoA-IV with CAD is independent of HDL cholesterol or triglycerides but

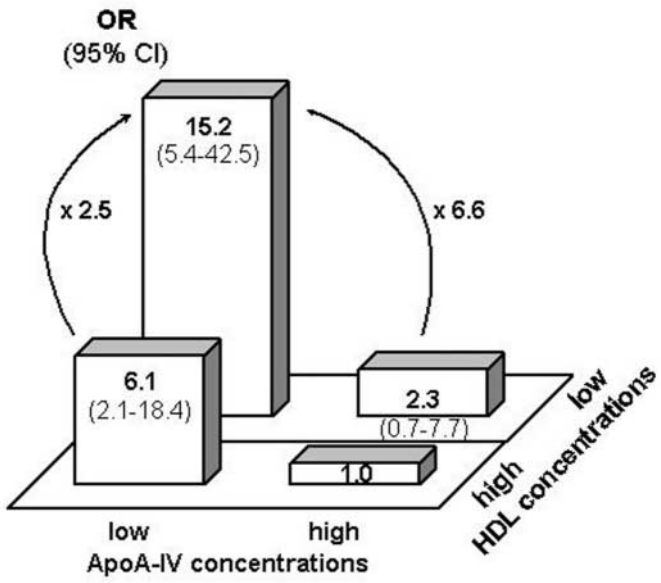

Fig. **3** Odds ratio (95% CI) for being a patient with coronary artery disease (CAD) in case of low or high plasma concentrations of apoA-IV and HDL cholesterol. The median levels of these variables from the control group were used as categorization cutpoints. Arrows provide the relative increase of the odds. Figure adapted from reference [37].

additive to their association with CAD which was confirmed by logistic regression analysis. It can therefore be concluded that the low apoA-IV concentrations are not simply a surrogate of low HDL cholesterol levels. This is in line with only a small correlation between the two parameters ($r^2 = 0.08$) and may reflect the observation from in vitro experiments that apoA-IV mostly forms distinct lipid-poor and apoA-I-free particles which are very effective mediators of cholesterol efflux [38, 39] and which are not assessed by the measurement of HDL cholesterol.

We confirmed the finding of 30% lower apoA–IV plasma concentrations in patients with CAD in an independent sample of Asian Indians with angiographically documented CAD and age-matched controls [37]. We even could extend the observation to patients with mild and moderate renal insufficiency [40]. In more detailed analysis of the plasma distribution of apoA-IV we observed no differences in the distribution of apoA-IV to the various lipoprotein fractions between CAD patients and controls. This suggests that the anti-atherogenic effect of apoA-IV is caused by other functional properties of apoA-IV (e. g.the antioxidative characteristics) [41].

Our data are supported by a recent study which observed an association between the S347 variant of the apoA-IV gene and coronary heart disease. This variant is also associated with lower apoA-IV plasma levels [42].

No study up to now investigated the association between apoA-IV concentrations and the risk for cardiovascular and cerebrovascular events in patients with PAD as well as the local progression of PAD.

Candidate genes for PAD

We plan to investigate several candidate genes for atherosclerosis in F3 and their association with PAD. These genes are mostly related to lipid metabolism, inflammation and coagulation. The exact selection of the genes and the single nucleotide polymorphisms to genotype will be decided at the time when the follow-up of the study is finished and depending on the latest results on candidate genes.

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