VELIPEKKA SUOMINEN

Clinical Features and Consequences of Peripheral Arterial Disease in Old Age

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ACADEMIC DISSERTATION
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CONTENTS

ABBREVIATIONS

ABI	ankle-brachial index
ACC	American College of Cardiology
ADL	activities of daily living
ADP	dorsal pedal artery
AHA	American Heart Association
AP	antero-posterior
CHD	coronary heart disease
COP	centre of pressure
COPD	chronic obstructive pulmonary disease
CTA	computed tomographic angiography
CVD	cerebrovascular disease
CW-Doppler	continuous wave Doppler
CLI	critical limb ischaemia
DM	diabetes mellitus
DSA	digital subtraction angiography
EC	eyes closed
ECG	electrocardiogram
ECQ	Edinburgh Claudication Questionnaire
EO	eyes open
ESRD	end-stage renal disease
EU	the European Union
IADL	instrumental activities of daily living
IC	intermittent claudication
ICD	International Statistical Classification of Diseases and Related Health Problems
ICF	International Classification of Functioning, Disability and Health
ICIDH	International Classification of Impairments, Disabilities and Handicaps
KTL	National Public Health Institute
ML	medio-lateral
MOS-SF 36	Medical Outcomes Survey SF-36
MRA	magnetic resonance angiography
PAD	peripheral arterial disease
PADL	physical activities of daily living
PVR	pulse volume recording
QoL	quality of life
SLP	segmental limb pressure
STAKES	National Reasearch and Development Centre for Welfare and Health
TASC	TransAtlantic Inter-Society Consensus
TAUH	Tampere University Hospital
TBI	toe-brachial index

TcPO2	transcutaneous oxygen tension
TIA	transient ischaemic attack
WD	walking distance
WHO	World Health Organization
WIQ	walking impairment questionnaire

GLOSSARY

Atherosclerosis	Hardening of an artery specifically due to chronic inflammatory response in the walls of arteries, in large parts due to the deposition of lipoproteins.
Disability	The inability to meet the expectations of a particular social role because of reduced physiological capasity associated with a health or physical problem.
Force platform	A device to measure postural balance quantitively.
Functional limitation	Restrictions in the ability to perform basic tasks of everyday life.
Functional impairment	System dysfunction; refers to a loss or abnormality at the organ (tissue) and body system level.
Functioning	Ability to perform basic tasks of everyday life.
Peripheral arterial disease	Narrowing or occlusion of the arteries supplying the lower extremities mainly caused by atherosclerosis.
Postural balance	The act of maintaining, achieving or restoring the line of gravity within the base of support.
Semi-tandem standing	Balance test position; the first metatarsal joint of one foot beside the calcaneus of the other foot.
Sway velocity	The displacement of COP during each second of a balance test on a force platform.
Tandem standing	Balance test position; feet positioned heel to toe along the midline of the platform.
Velocity moment	The first moment of velocity calculated as the mean area covered by the movement of COP during each second of a test on a force platform.
Walking endurance	A test to measure lower extremity functional status. The test is conducted in a long corridor and the participant is instructed to walk (usually) for six minutes.

Walking velocity	Walking speed; a test to measure lower extremity functional status; usually assessed by walking a 2.4–10-metre distance at normal and maximal pace.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in the text by their Roman numerals:

I Suominen V, Rantanen T, Venermo M, Saarinen J and Salenius J. Prevalence and risk factors of PAD among patients with elevated ABI. Eur J Vasc Endovasc Surg 2008; 35: 709–714.

II Velipekka Suominen, Taina Rantanen, Eino Heikkinen, Maarit Heikkinen and Juha Salenius. Peripheral arterial disease and its clinical significance in nonagenarians. Aging Clin Exp Res 2008; 20: 211-215.

III Velipekka Suominen, Juha Salenius, Eino Heikkinen, Maarit Heikkinen and Taina Rantanen. Absent pedal pulse and impaired balance in older people: a cross-sectional and longitudinal study. Aging Clin Exp Res 2006; 18: 388–393.

IV Velipekka Suominen, Juha Salenius, Päivi Sainio, Antti Reunanen and Taina Rantanen. Peripheral arterial disease, diabetes, and postural balance among elderly Finns: population-based study. Aging Clin Exp Res, in press.

ABSTRACT

The risk factors, typical symptoms (intermittent claudication, critical limb ischaemia) and treatment of peripheral arterial disease (PAD) are widely studied and well-known to clinicians. The role of elevated ankle-brachial index (ABI) in the process of diagnosing PAD and the prevalence and clinical features of PAD in nonagenarians are, however, unknown. In addition, the relationship between PAD and functional decline has attracted little attention until recently. We therefore began to pursue more knowledge about factors underlying or indicating PAD in older people and to describe functional decline in peripheral arterial disease.

The association of elevated ABI and PAD was assessed in a clinical sample of 1,762 patients admitted to the vascular outpatient clinic by comparing the ABI and TBI results, in addition to determining further which factors were significantly associated with PAD among those with elevated ABI. The role of PAD among nonagenarians was evaluated in a cohort of 90-year-old individuals (N=58) by measuring ABI and inquiring about their mobility level. In a subgroup of participants, lower extremity functional status was measured by performing walking tests. The association of PAD and mortality among nonagenarians was also assessed during a one-year follow-up. The relationship between PAD and impaired balance was evaluated both cross-sectionally and longitudinally by using standardized force platform balance tests. The results of two population-based studies (The Evergreen project [N=419] and the Health 2000 survey [N=1323]) were analyzed for this purpose.

The prevalence of elevated ABI among patients admitted to the vascular outpatient clinic was 8.4% and that of PAD among them 62%–84% depending on the cut-off value (1.3–1.5). PAD was significantly more probable among those with chronic renal failure, a history of smoking and coronary heart disease (CHD). The specificity of elevated ABI ($\geq$ 1.3) in identifying patients with PAD seems to be good, whereas its sensitivity in excluding the disease is only satisfactory. Among nonagenarians, PAD was mainly asymptomatic, with a prevalence of 22%. Moreover, approximately one third of them presented with elevated ABI. Nonagenarians with a low (<0.9) or high (>1.4) ABI reported more difficulties in the physical activities of daily living (PADL tasks) than those with normal ABI, but the results did not reach statistical significance. Furthermore, an abnormal ABI was shown to correlate with poorer one-year survival among the subjects. The results also implied that PAD is associated with poorer balance performance both cross-sectionally and longitudinally. In the cross-sectional analysis, the presence of diabetes exacerbated the deterioration in balance but alone affected balance somewhat less than PAD.

The utility of ABI in diagnosing PAD seems to be more wide-ranging than the traditional conception presumes. In addition, PAD, even though mainly asymptomatic, continues to affect the life of nonagenarians. However, more studies are required to determine the possible relationship between PAD and mobility loss in very old people. The fact that PAD is associated with poorer

balance gives the clinician a tool for recognizing those possibly at greater risk for mobility loss and nursing home placement.

1 INTRODUCTION

Peripheral arterial disease (PAD) is defined as a narrowing or occlusion of the arteries supplying the lower extremities. The major cause of PAD is atherosclerosis. A resting ankle-brachial index (ABI) of ≤ 0.9 is caused by haemodynamically significant arterial stenosis and is most often used in epidemiological studies as a threshold value for the presence of PAD (TASC working group 2007). The overall prevalence of PAD steadily increases from the age of 50 onwards and is in the range of 3% to 18%, increasing to 25% to 30% in persons over 75 years (Stoffers et al. 1996, Meijer et al. 1998, Hirsch et al. 2001, Aronow et al. 2002, Diehm et al. 2004, Heidrich et al. 2004, Selvin and Earlinger 2004, Ostchega et al. 2007, Sigvant et al. 2007). These figures also include asymptomatic patients but with a diminished ABI. It has been estimated, that, actually, only roughly one third of PAD patients exhibit typical symptoms (intermittent claudication [IC], critical limb ischaemia [CLI]) and that the majority are asymptomatic (Stoffers et al. 1996, McDermott et al. 2000, Hirsch et al. 2001, Sigvant et al. 2007).

The role and significance of elevated ABI in the process of diagnosing PAD is unknown, and only limited information is available on the prevalence of cardiovascular diseases in the very old (those over 90 years of age). Furthermore, the consequences of PAD in terms of physiological impairments and functional limitations have attracted little attention until recently (Hiatt et al. 1995, McDermott et al. 1998a, McDermott et al. 1998b, McDermott et al. 1999, McDermott et al. 2006a, McDermott et al. 2007a).

Today, no uniform ABI criterion exists for elevated ABI. While some authors have recommended that high ABI should be suspected when ABI exceeds 1.15, others have used the cut-off value between 1.3 and 1.5 (Goss et al. 1989, Takolander and Rauwerda 1996, Meijer et al. 1998, Leskinen et al. 2002, Begelman and Jaff 2006). Consequently, the prevalence has also varied to a great degree from less than 1% to up to 13.6% and even higher among diabetic patients (Goss et al. 1989, Meijer et al. 1998, Diehm et al. 2004, Stein et al. 2006). Although the association between high ABI and total and cardiovascular mortality is similar to that of low ABI, the association between elevated ABI and PAD is unknown (Resnick et al. 2004, O'Hare et al. 2006). According to available literature, the prevalence of cardiovascular diseases among nonagenarians ranges between 42% and 78% (von Strauss et al. 2000, Goebeler et al. 2003). However, the prevalence and clinical features of PAD in nonagenarians have not been studied in detail.

Functional ability, or functioning, refers to the ability to perform basic tasks of everyday life (Satariano 2005, p. 125). The capacity of the individuals on the one hand and the resources and demands of the social and physical environments on the other define the level and ease of functioning. The measures of functional ability are usually based on ordinal, interval or continuous scales and physical performance measures. Functioning therefore provides a more comprehensive and complete picture of the health and well-being of an individual than other public health statistics with dichotomous classification (Satariano 2005, p. 130).

Variation in the measurements of functional limitation can, however, lead to inconsistency in the results and consequently restricts cross-study comparison (Johnson and Wolinsky 1993, Boult et al. 1994). Therefore, a universal language, such as the disablement model, with which to discuss functioning and disability is needed.

The two conceptual disablement frameworks that have received widespread use in the research of the epidemiology of aging and disability are the disablement model developed by Nagi in 1976 and later elaborated by Verbrugge and Jette (Nagi 1976, Verbrugge and Jette 1994), and the current version of the International Classification of Impairments, Disabilities and Handicaps (ICIDH) (World Health Organization 1980) known as the International Classification of Functioning, Disability and Health (ICF) (World Health Organization 2001). Both of these frameworks represent the contemporary biopsychosocial view of the phenomenon of disability, describing it as a consequence of biological, personal, environmental and social forces.

The ability to walk and climb stairs without assistance, i.e. a person's mobility, reflects the functional status of lower extremities and, more extensively, the person's ability to function independently in the community (Patel et al. 2006). Mobility difficulties are common in older people and increase with age. They represent a critical stage in the disablement process as they predict disability, nursing home placement and mortality (Guralnik et al. 1994, Guralnik et al. 1995, Rantanen et al. 1999, Guralnik et al. 2000). Although intermittent claudication as such may restrict an individual's ability to cope with the demands of everyday life, the relationship between PAD and functional decline has attracted little attention until recently.

The present study was undertaken to investigate factors underlying or indicating PAD in older people and to describe functional decline in peripheral arterial disease.

2 REVIEW OF THE LITERATURE

The references cited in the original publications and the essential text books related to the topic of the thesis formed the basis for this review. Additional references were sought by perfoming a PubMed search using terms “balance impairment”, “disablement process”, “elevated ABI”, “functional ability”, “functional decline”, “functional limitation”, “lower extremity function”, “nonagenarians”, “periheral arterial disease” and their various combinations. The initial search was performed in October 2007 without a time limit, and the search was repeated in April 2008. The most appropriate and recent articles were selected for the review.

2.1 Peripheral arterial disease

Peripheral arterial disease (PAD) is defined as a narrowing or occlusion of the arteries supplying the lower extremities. A resting ankle-brachial index (ABI) of ≤ 0.9 is caused by haemodynamically significant arterial stenosis and is most often used in epidemiological studies as a threshold value for the presence of PAD (TASC working group 2007). The major cause of PAD is atherosclerosis. Other conditions that can result in PAD include inflammatory or aneurysmal disease as well as trauma, adventitial cysts, entrapment syndrome or congenital abnormalities.

Along with the ageing of the Western population, the prevalence of degenerative, i.e. atherosclerotic, PAD is also increasing. This is bound to increase the work load and expenditure of public health services, as PAD is associated with high cardiovascular morbidity and mortality due to atherothrombotic events, in addition to being related to a deterioration in the quality of life (Leng et al. 1996a, Criqui et al. 1997, Ness and Aronow 1999, Diehm et al. 2004). It is therefore desirable to establish an accurate diagnosis for an individual patient and to offer appropriate pharmacological treatment together with possible endovascular, surgical and rehabilitative interventions as early as possible. Unfortunately, this is not always the case, as a high rate of undiagnosed PAD is demonstrated in primary care practice (Hirsch et al. 2001, Diehm et al. 2004).

2.1.1 Epidemiology

The overall prevalence of PAD steadily increases from the age of 50 onwards and is in the range of 3% to 18%, increasing to 25 to 30% in persons over 75 years (Stoffers et al. 1996, Meijer et al. 1998, Hirsch et al. 2001, Aronow et al. 2002, Diehm et al. 2004, Heidrich et al. 2004, Selvin and Earlinger 2004, Ostchega et al. 2007, Sigvant et al. 2007). It has been estimated that only roughly one third of PAD patients exhibit typical symptoms (intermittent claudication [IC], critical limb ischemia [CLI]) and the majority are asymptomatic (Stoffers et al. 1996, McDermott et al. 2000, Hirsch et al. 2001, Sigvant et al. 2007). This is an important detail, as asymptomatic patients have the same risk of

cardiovascular events as their symptomatic counterparts (Leng et al. 1996a, Hirsch et al. 2001, Diehm et al. 2004). Traditionally, PAD is considered more common in men. This is still true for the younger patients, but the differences level out after the age of 70 (Diehm et al. 2004). In a recent study by Sigvant and co-authors, the prevalence of PAD was found to be higher among women when the definition was based solely on ABI (Sigvant et al. 2007).

The prevalence of IC varies between 1% and 7% and clearly depends on the study design and methods used to define PAD (Reunanen et al. 1982, Fowkes et al. 1991, Bainton et al. 1994, Stoffers et al. 1996, Meijer et al. 1998, He et al. 2006, Sigvant et al. 2007). In the Edinburg Artery Study utilizing the Edinburg Claudication Questionnaire (ECQ), a modification of the WHO / Rose questionnaire, the authors found a 4.6% prevalence of PAD among patients aged 55–74 (Rose et al. 1982, Fowkes et al. 1991). The WHO / Rose questionnaire was used in the Rotterdam study to assess the prevalence of IC in 7,715 participants (Meijer et al. 1998). Only 1.6% of the participants reported IC, and the prevalence varied from 0.7% in women aged 55 to 59 years to 6.0% in men aged 85 and older. Of those who were found to have an ABI < 0.9, i.e. PAD, 6.3% reported symptoms of PAD. Diehm and colleagues used a quite similar study design on 6,880 primary care patients aged over 65 years and found the prevalence of IC to be approximately 3% (Diehm et al. 2004). In the same study, the prevalence of PAD as indicated by an ABI < 0.9 was 19.8% for men and 16.8% for women, thus underlining the asymptomatic nature of PAD. By using ABI < 0.9 as a diagnostic criterion for PAD, a large Swedish population-based study – the most recent on this subject – established the prevalence of IC of 7% (Sigvant et al. 2007).

There is little information on the actual prevalence and incidence of CLI. Depending on the calculation method, the annual incidence of CLI is approximately 300–600 new cases every year per one million people (Catalano 1993, The Vascular Surgical Society of Great Britain and Ireland 1995, TransAtlantic Inter-Society Consensus 2000). Some calculations are based on the progression of the disease from IC to CLI: using a claudication prevalence of 3% and assuming that 5% of these will deteriorate to CLI, the incidence of CLI is approximately 300 per one million inhabitants (TransAtlantic Inter-Society Consensus 2000). In 1993 Catalano published his data on the incidence of CLI, which was calculated using three different methods: 1) progression of IC to CLI in a prospective 7-year follow-up among 200 claudication patients and 190 controls; 2) CLI-hospitalizations during a prospective three-month sample; 3) a 6-month to 2-year encoding of major amputations in two regions (Catalano 1993). The annual incidence of CLI varied from 530 per one million people among those who required major amputation to 652 per one million people among those who were hospitalized due to CLI. The aforementioned Swedish study is among the first to describe the prevalence of CLI by means of population-based identification (Sigvant et al. 2007). By defining CLI as < 70 mmHg in ankle blood pressure, a prevalence of 1.2% was found. By adding the information of possible rest pain to the definition, the prevalence of CLI dropped to 0.5%.

2.1.2 Risk factors

Since PAD is mainly caused by atherosclerosis, classic risk factors for atherosclerosis such as male sex, old age, diabetes, cigarette smoking, dyslipidaemia, hypertension, hypercoagulable states and hyperhomocystenemia increase the likelihood of developing PAD (Figure 1). There is also evidence suggesting that ethnic background has a role in the evolution and progress of PAD (Kullo et al. 2003, Selvin and Earlinger 2004). Kullo and co-authors found that African-Americans, even after adjusting for age and conventional risk factors, suffer more frequently from PAD than non-Hispanic white individuals. Similar results were achieved by Selvin and colleagues in their study on 2,174 participants aged 40 years and over. In addition to non-Hispanic black individuals, the National Health and Nutrition Survey showed that Mexican-American women had a higher prevalence of PAD compared to non-Hispanic white individuals (Ostchega et al. 2007). The most prominent risk factors of PAD include advancing age, smoking and diabetes.

Smoking is the single most important risk factor for the development of PAD. The relationship was first described by Erb in 1911, when he reported a three-fold increase in the incidence of IC among smokers compared to non-smokers (Erb 1911). Subsequently, many epidemiological studies have confirmed this finding with the relative risk ratios ranging from 1.7 to 7.5 (Hughson et al. 1978, Schroll and Munck 1981, Reunanen et al. 1982, Gofin et al. 1987, Criqui et al. 1989, Murabito et al. 1997).

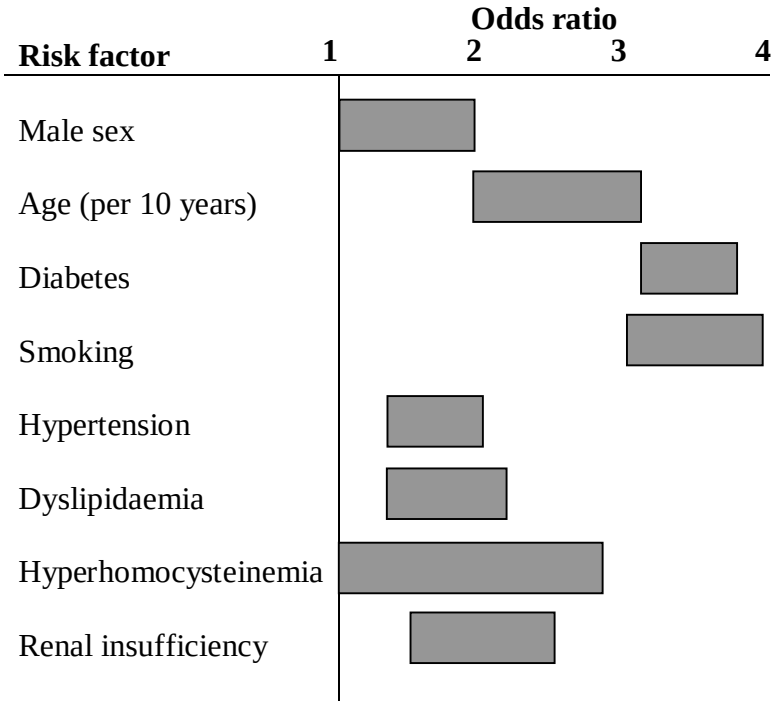


Figure 1. Range of odds ratios for the risk factors for symptomatic peripheral arterial disease. (Modified from: TASC working group 2007).

When PAD is defined as ABI < 0.9, current smokers are in 2.5-fold risk for developing PAD (Newman et al. 1993). Additionally, cigarette smoking increases the risk of PAD in both sexes; and the prevalence and severity of PAD appear to increase with the number of cigarettes smoked (Kannel and McGee 1985, Willigendael et al. 2004, Eason et al. 2005). Smoking cessation rapidly lowers the incidence of IC, whereas those who continue to smoke after peripheral vascular bypass surgery have a very high amputation and mortality rate (Lassila and Lepäntalo 1988, Ameli et al. 1989, Ingolffson et al. 1994, TransAtlantic Inter-Society Consensus 2000).

Diabetes mellitus is highly associated with PAD and its progression (Gordon and Kannel 1972, Stout 1990). In a primary care setting, approximately 30% of PAD patients suffer from diabetes, and the figure increases to up to 40% among those requiring hospitalization due to PAD (Diehm et al. 2004, McDermott et al. 2004a, Sukhija et al. 2005). Overall, diabetes increases the risk of developing IC two-fold, and PAD in general, three to four-fold (Kannel and McGee 1985, Newman et al. 1993, Ingolffson et al. 1994, Murabito et al. 1997). Among patients with IC, those suffering from diabetes are at a greater risk of developing CLI, especially gangrene (Jonason and Ringqvist 1985). Consequently, individuals with diabetes have a seven to ten-fold risk of major amputation compared to non-diabetic patients (Hughson et al. 1978, Jonason and Ringqvist 1985, Newman et al. 1993). Moreover, for every 1% increase in haemoglobin A1c, there is a corresponding 26% increased risk of PAD in type 2 diabetes (Selvin et al. 2004). It is, however, unclear whether aggressive blood-glucose lowering will protect peripheral circulation and prevent amputation (TASC working group 2007). Current evidence further suggests that insulin resistance even without diabetes raises the risk of PAD by approximately 40% to 50% and that hyperinsulinemia is an additional risk factor for PAD (Criqui et al. 1989, Price et al. 1996, Muntner et al. 2005).

There have been conflicting reports on the relationship between hypertension and PAD. The Framingham heart study and the Cardiovascular Heart Study both found a clear association between high blood pressure and PAD (Newman et al. 1993, Murabito et al. 1997). More recently, Ness and Aronow reported a 2.2-fold risk of PAD among elderly men with hypertension and a 2.8-fold risk in elderly women (Ness and Aronow 2000). On the other hand, the study by Reunanen and co-authors showed no significant relationship between hypertension and IC (Reunanen et al. 1982).

Dyslipidaemia is associated with the development and progression of PAD and its complications, but the role is less clear-cut compared to smoking and diabetes. The Framingham heart study found that higher cholesterol levels (>270 mg/100 ml) were associated with a doubling of the frequency of IC (Murabito et al. 1997). In the Cardiovascular Heart Study, the risk of developing PAD increased by 10% for each 10 mg/100 ml increment in total cholesterol (Newman et al. 1993). At the same time, a number of studies do not confirm this association (Hughson et al. 1978, Zimmerman et al. 1981, Criqui et al. 1989). There is, however, accumulating evidence that treatment of hyperlipidaemia reduces both the progression of atherosclerosis in the peripheral arteries and the

incidence of intermittent claudication (Duffield et al. 1983, The Lipid Research Clinics Coronary Primary Prevention Trial results I 1984, Youssef et al. 2002, de Sauvage Nolting et al. 2003). Three other studies support these results, as the authors were able to demonstrate that statins improve walking performance in persons with PAD (Aronow et al. 2003, Mohler et al. 2003, Mondillo et al. 2003). Lastly, an association between PAD and hypertriclyceridemia has been reported, but this association is still debatable (Reunanen et al. 1982, Gofin et al. 1987, Criqui et al. 1989, Brevetti et al. 2006).

Due to the conflicting results, the role of hyperhomocysteinaemia as a risk factor for PAD is uncertain. Earlier studies showed that hyperhomocysteinaemia serves as an independent risk factor for cardiovascular disease in general and for PAD in particular (Boushey et al. 1995, Nygård et al. 1997). However, no relationship between total plasma homocysteine level and lower extremity arterial disease was found in two more recent prospective studies (Folsom et al. 1998, Ridker et al. 2001).

Furthermore, the role of elevated plasma levels of fibrinogen as a risk factor for PAD has been demonstrated in several studies (Kannel et al. 1987, Kannel et al. 1992). Inflammation risk markers, such as C-reactive protein and soluble cellular adhesion molecules constitute yet another risk factor for PAD (Rohde et al. 1998, Ridker et al. 2001, Bloemenkamp et al. 2002, Pradhan et al. 2002). These markers are valuable to be measured as risk factors in healthy subjects. Owing to the current technologies, CRP is perhaps a more useful tool for screening. Finally, there is also evidence of an association between PAD and renal insufficiency, especially in postmenopausal women and in those receiving dialysis (Leskinen et al. 2002, O'Hare et al. 2004, O'Hare et al. 2005)

2.1.3 Co-existing vascular disease

PAD is the third most important manifestation of atherosclerotic disease along with coronary heart disease (CHD) and cerebrovascular disease (CVD). Consequently, given the systemic nature of atherosclerosis, persons with PAD commonly have coexistent arterial obstructive disease in other vascular territories (Figure 2). In addition to CHD and CVD, the prevalence of renal artery stenosis among patients with PAD has been studied. The prevalence of renal artery stenosis of at least 50% is 3% in the general population, in comparison to the 23%–42% among those with PAD (TASC working group 2007).

The prevalence of CHD among those with PAD depends upon the method used to establish the diagnoses. History, clinical examination and electrocardiogram (ECG) identify a prevalence of CHD in 40% to 60% of those with a clinical history of PAD (Dormandy et al. 1989, Fowkes et al. 1991, Aronow and Ahn 1994). According to the available literature, fewer than 10% of those requiring surgical intervention for PAD have normal coronary arteries in angiography, and an at least 50% stenosis can be found in roughly 60% of patients (Hertzer et al. 1984). In the PARTNERS study, 16% of subjects had an ABI < 0.90 as well as symptomatic CHD or CVD (Hirsch et al. 2001). There is a

distinct association between ABI and the severity of CHD, as Sukhija and co-authors found that among those with an ABI < 0.4, the prevalence of 3- or 4-vessel CHD was 84%, whereas the prevalence among those with an ABI of 0.70–0.89 was only 26% (Sukhija et al. 2005).

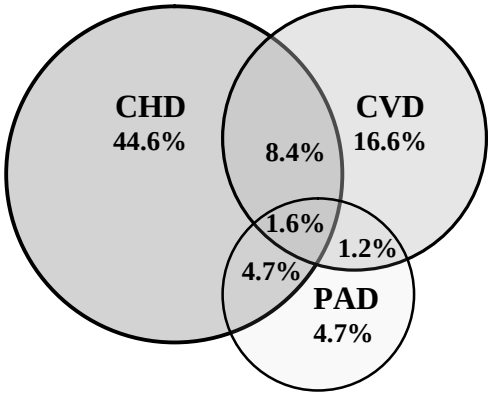


Figure 2. Distribution of the three main manifestations of atherosclerosis (CHD= coronary heart disease, CVD=cerebrovascular disease, PAD=peripheral arterial disease). (Modified from: Bhatt et al. 2006).

The association of PAD with CVD is significant but seems to be weaker than with CHD. Carotid artery disease occurs in one quarter to half of the patients with IC when examined by duplex (Boushey et al. 1995). However, the prevalence of ischaemic stroke or transient ischaemic attack (TIA) in patients with PAD is only some 10% to 14%, increasing to over 30% among elderly individuals in long-term care institutions (Aronow and Ahn 1994, CAPRIE steering committee 1996, Hirsch et al. 2001).

PAD, regardless of the symptoms, has been associated with increased cardiovascular morbidity and mortality (Leng et al. 1996b, Diehm et al. 2004). The risk of total and cardiovascular mortality among those with an ABI < 0.9 is between 1.5 and 1.8 compared to those with normal ABI; the annual overall major cardiovascular event rate for PAD patients is approximately 5%–7% (Newman et al. 1993, Leng et al. 1996b, TASC working group 2007). For patients with CLI, the prognosis is even worse, as their mortality rate is approximately 20% during the first year after presentation (TASC working group 2007). ABI level has been shown to be a good predictor of cardiovascular events in an unselected general population, and some studies suggest that this relationship is almost linear (Fowkes et al. 1991, Mehler et al. 2003). In the Strong Heart Study, the association between ABI and all-cause and cardiovascular mortality was found to be U-shaped, suggesting that those with a high ABI (> 1.4) are at a similar risk as those with a low ABI (< 0.9) (Figure 3) (Resnick et al. 2004). This finding was later supported by the results of the Cardiovascular Health Study (O'Hare 2006).

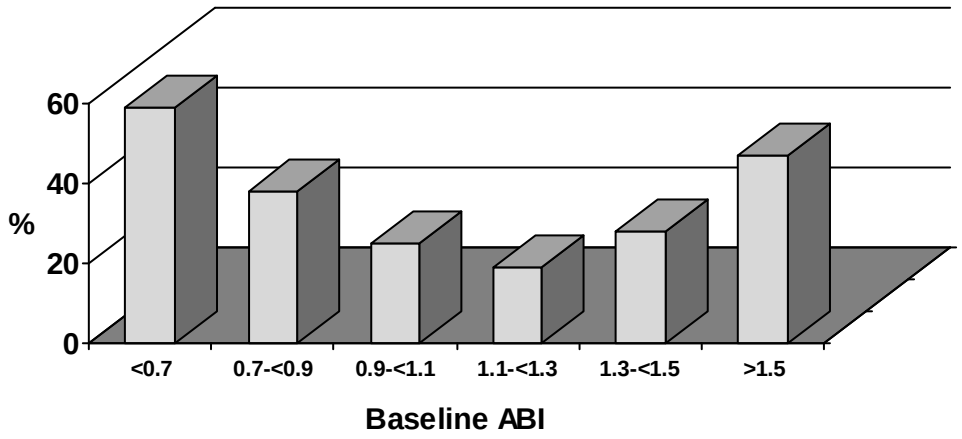


Figure 3. All-cause mortality according to baseline ABI. (Modified from: Resnick et al. 2004).

2.1.4 Peripheral arterial disease and other atherosclerotic manifestations in nonagenarians

Along with the overall ageing of the population, there is also a clear increase in the number of individuals who reach a very high age (over 90 years of age). In the EU, the proportion of individuals aged over 80 is expected to rise by 45% between 2004 and 2020 (Eurostat 2005). In Finland, during the same period, a 60% rise in the number of individuals aged over 90 is anticipated (Statistics Finland 2005: Population Statistics: Demographics). At the same time, the life expectancy of people at a very advanced age is growing and is more than four years even for nonagenarians (Statistics Finland 2005: Population projection by age group).

The prevalence and clinical features of PAD in nonagenarians has not been studied in detail. In previous studies on the prevalence of PAD, the highest age groups have usually been over 65, 80 or 85 years old, and the results show an overall prevalence of PAD in the range of 20% to 50% and even higher, depending on the study design (Meijer et al. 1998, Hirsch et al. 2001, Diehm et al. 2004, Heidrich et al. 2004). According to these studies, the prevalence steadily increases from the age of 50 onwards and peaks at the age of 85 and over**.**

During the last ten years, there has been an increasing interest in nonagenarians as well as their morbidity and co-morbidity, functional status and longevity in general (von Strauss et al. 2000, Goebeler et al. 2003, Nybo et al. 2003, Kevorkian et al. 2004, Rontu et al. 2006, Lehtimäki et al. 2007). The actual prevalence of cardiovascular diseases among nonagenarians is not known, but, according to the scant literature available on the subject, ranges between 42% and 78% (von Strauss et al. 2000, Goebeler et al. 2003). These figures are supported by the finding that almost 30% of the hospital discharge diagnoses of nonagenarians are cardiovascular diseases (Goebeler et al. 2004). Furthermore, autopsy studies on nonagenarians and centenarians show that cardiovascular diseases are the most common cause of death among them (John and Koelmeyer

2001, Berzlanovich et al. 2005). The study by Nybo and colleagues shows that in nonagenarians, the consequences of extremely old age and longlasting diseases such as disability, poor physical and cognitive performance as well as low self-rated health, rather than individual diseases as such, are the most important predictors of mortality (Nybo et al. 2003).

The question of secondary prevention of atherosclerosis among nonagenarians is controversial and has received little scientific attention. At the same time, polypharmacy among individuals of an extremely high age is common and is often accompanied by complications (Hanlon et al. 1997, Fialova et al. 2005, Simon et al. 2005). According to the criteria suggested by Beers and updated by Fick in 2003, there are currently 48 potentially inappropriate drugs, some of which should never be used for the elderly (Beers 1997, Fick et al. 2003). This also concerns antithrombotic agents especially when used together with anticoagulant therapy.

Finally, according to the limited data, nonagenarians seem to tolerate carotid and cardiac surgery as well as endovascular cardiac and aortic procedures well (Bacchetta et al. 2003, Durward et al. 2005, Moreno et al. 2004, Baril et al. 2006). While in favour of active surgical and endovascular treatment of cardiovascular diseases in nonagenarians, all authors underline the importance of careful patient selection – only the fittest are considered fit for invasive procedures.

2.1.5 Clinical manifestations

The first clinical classification of peripheral arterial disease was introduced by Fontaine in 1954, dividing PAD into four stages (Table 1) (Fontaine et al. 1954). Stage I patients are considered asymptomatic as they do not present with symptoms of intermittent claudication or critical limb ischaemia. Stage II patients have manifest IC; according to walking distance, this stage is subdivided into stage IIa (walking distance [WD] > 200 metres) and IIb (WD < 200 metres) (TransAtlantic Inter-Society Consensus 2000). In stage III patients present with rest pain, and stage IV is characterized by the appearance of ulcerations and/or gangrene.

Recently, Rutherford has proposed an alternative classification with six clinical categories; the use of this more recent classification is encouraged by the Trans-Atlantic Inter-Society Consensus (TASC) Working Group (Table 1) (Rutherford et al. 1997, TransAtlantic Inter-Society Consensus 2000). Although the two classification systems are commonly used to rate the symptom severity and assess the benefits of interventions, both have limitations in routine use, as they do not necessarily recognize the aetiology of a particular symptom (ischaemic vs. spinal claudication, ischaemic vs. neuropathic pain) (Rudofsky 2002).

Table 1. Classification of peripheral arterial disease: Fontaine's stages and Rutherford's Categories.

FONTAINE		RUTHERFORD		
Stage	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate-severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischaemic rest pain	II	4	Ischaemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		IV	6	Ulceration or gangrene

2.1.5.1 Asymptomatic disease

As mentioned, the majority of the patients with PAD are asymptomatic. Asymptomatic disease, however, carries the same risks of cardiovascular morbidity and mortality, and therefore early detection by clinical examination and, especially, by measurement of the ABI is essential. According to the TASC recommendation, PAD should be ruled out in all individuals over 70 years of age regardless of their co-morbidities, and even earlier among those with diabetes and other risk factors for PAD (TASC working group 2007). Although asymptomatic patients may not have typical intermittent claudication, they often present with atypical symptoms and diminished lower extremity function (McDermott et al. 2000, McDermott et al. 2001a, McDermott et al. 2004a).

2.1.5.2 Intermittent claudication

The classic symptom of peripheral arterial disease is intermittent claudication, which is aching muscle pain in the lower limb during exercise. The term claudication is derived from the Latin word *claudicatio*, which translates as "to limp". If exercise is continued, the pain increases and usually forces the patient to stop. Typically, ishaemic pain is relieved within 10 minutes of rest (TASC working group 2007). The pain, or discomfort, during exercise is caused by lactic acid and other metabolites, which are produced in muscles under anaerobic conditions as a result of a mismatch between oxygen supply and muscle metabolic demand in ambulating patients (Meru et al. 2006). The most common symptom is calf muscle pain, but symptoms may also affect the thigh or buttocks. In addition to PAD, there are several other diseases that may cause exertional leg pain (Table 2). The diagnosis of vascular claudication can usually be established by measuring the ABI. If the ABI is normal (0.91 to 1.30) or elevated (>1.30) and vascular claudication is suspected, other methods, such as the toe-brachial index, segmental pressure examination, and duplex ultrasound, should be used to confirm the diagnosis (Hirsch et al. 2006).

The prognosis of IC regarding the leg is good. Only some 5%–10% of the patients will develop CLI during the first five years after the diagnosis, and only 1%–2% will ever require major amputation (Dormandy et al. 1989, TransAtlantic Inter-Society Consensus 2000, TASC working group 2007). At the

Table 2. Differential diagnosis of intermittent claudication (IC). (Modified from: TASC working group 2007).

Condition	Location	Characteristic	Effect of exercise	Effect of position	Other characteristics
Calf IC	Calf muscles	Cramping, aching discomfort	Reproducible onset	None	May have atypical limb symptoms on exercise
Thigh and buttock IC	Buttocks, hip, thigh	Cramping, aching discomfort	Reproducible onset	None	Impotence May have normal pedal pulses with isolated iliac artery disease
Foot IC	Foot arch	Severe pain on exercise	Reproducible onset	None	Also may present as numbness
Chronic compartment syndrome	Calf muscles	Tight, bursting pain	After much exercise (jogging)	Relief with elevation	Typically heavy muscled athletes
Venous claudication	Entire leg, worse in calf	Tight, bursting pain	After walking	Relief speeded by elevation	History of iliofemoral deep vein thrombosis, signs of venous congestion, oedema
Nerve root compression	Radiates down leg	Sharp lancinating pain	Induced by sitting, standing or walking	Improved by change in position	History of back problems Worse with sitting Relief when supine or sitting
Symptomatic Bakers cyst	Behind knee, down calf	Swelling, tenderness	With exercise	None	Not intermittent
Hip arthritis	Lateral hip, thigh,	Aching discomfort	After variable degree of exercise	Improved when not weight bearing	Symptoms variable History of degenerative arthritis
Spinal stenosis	Often bilateral buttocks, posterior leg	Pain and weakness	May mimic IC	Relief by lumbar spine flexion	Worse with standing and extending spine
Foot/ankle arthritis	Ankle, foot, arch	Aching pain	After variable degree of exercise	May be relieved by not bearing weight	Variable, may relate to activity level and present at rest

same time, the fate of the patient is considerably worse due to the systemic character of atherosclerosis. It has been estimated that approximately 20% of the patients with IC die within five years of the diagnosis from myocardial infarction or stroke; another 5%–10% will suffer nonfatal cardiovascular events (Newman et al. 1993, Leng et al. 1996b, TASC working group 2007).

2.1.5.3 Critical limb ischaemia

When blood flow is inadequate to meet the metabolic demands of the resting tissue, peripheral arterial disease manifests in rest pain or in the breakdown of the skin in the affected limb. This corresponds with Fontaine's classification stages III and IV or Rutherford's classification categories 4–6 (Table 1). Contrary to intermittent claudication, patients with CLI will most probably loose their limb within six months of the diagnosis if revascularisation is not offered or possible (Hirsch et al. 2006).

During the past two decades, there have been a a few attempts to define CLI more exactly, as the traditional classifications were found inadequate. In 1991 European vascular specialists prepared a Consensus document on CLI, which took into account both clinical symptoms and objective pressure measurements (Second European Consensus Document on Chronic Critical leg ishaemia, 1991). A similar definition was produced by the Ad Hoc Committee in 1997 (Rutherford et al. 1997). Both classifications used absolute ankle and toe pressures (50–60 mmHg and 30–40 mmHg, respectively) rather than the ABI to define CLI, as they were considered more relevant for the outcome of the leg (Rutherford et al. 1997). The strict absolute pressure limits have subsequently been abandoned: according to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II), the term CLI should be used in relation to patients with chronic ishaemic disease, defined as the presence of symptoms for more than two weeks with objectively proven arterial disease (TASC working group 2007). It was further emphasized that complete consensus regarding the vascular haemodynamic parameters to diagnose CLI currently does not exist.

2.1.6 Diagnosis

The diagnosis of PAD should be based on complete medical history, a physical examination and objective testing. A presumptive diagnosis can often be made on the basis of symptoms and pulse palpation (McGee and Boyko 1998, Schmieder and Comerota 2001). In younger patients, with no PAD risk factors, pulse palpation enables physicians to exclude the diagnosis of PAD with a high degree of certainty (Stoffers et al. 1997).

In most cases, however, objective assessment methods are mandatory and should be offered to 1) all individuals with exertional leg symptoms, 2) all patients between aged 50–69 with cardiovascular risk factors, 3) all patients aged $\geq$ 70 years regardless of risk factor status and 4) all patients with a Framingham risk score of 10%–20% (TASC working group 2007). Imaging is indicated if

some sort of revascularisation is planned; angiography still being the method of choice despite the availability of more recent technologies (Schmieder and Comerota 2001, Novo et al. 2004, TASC working group 2007).

2.1.6.1 Physical examination

The physical examination assesses the patient as a whole but should centre on the circulatory system. The general examination includes blood pressure measurement in both arms, cardiac auscultation and palpation for abdominal aortic aneurysm (TASC working group 2007). The evaluation of the extremities starts with an inspection for trophic changes due to PAD, such as hair loss, dry and shiny skin as well as and thickened nails; depending on the level of activity, muscle atrophy may be apparent, and patients with CLI may present with an ulcer or gangrene as well as with oedema of the foot (Schmieder and Comerota 2001, TASC working group 2007). The physical examination is completed with the palpation of the pulses at the base of the neck and in both the upper and lower extremities accompanied by auscultation when appropriate.

2.1.6.1.1 Pulse palpation

The role and the validity of pulse palpation in the process of diagnosing PAD has been widely studied, but the results are conflicting (Christensen et al. 1989, Hiatt et al. 1990, Brearley et al. 1992, Magee et al. 1992, Boyko 1997, Stoffers et al. 1997, McGee and Boyko 1998, Lundin et al. 1999, Collins et al. 2006, Khan et al. 2006, Cournot et al. 2007). Some authors have concluded that absent pedal pulses on palpation provide valuable information on the presence of PAD, and, on the other hand, palpable pulses enable physicians to exclude the diagnosis of PAD with a high degree of certainty (Christensen et al. 1989, Boyko et 1997, Stoffers et al. 1997, Khan et al. 2006, Cournot et al. 2007). At the same time, others have concluded quite the contrary: in a resent study by Collins and colleagues on 403 primary care patients, the sensitivity of pulse palpation to detect PAD was between 18%–32% (Collins 2006). Furthermore, inter-observer agreement on pulse palpation has been found to be low (Lundin et al. 1999, Magee et al. 1992). Some investigators, while questioning the reliability of pedal pulse palpation, have shown training to improve the results (Brearley et al. 1992).

In addition to PAD and observer error, foot pulses may be congenitally absent, or local conditions such as oedema may disturb the evaluation. The prevalence of absent foot pulses due to a previous vascular trauma is likely to be very low; however, no estimates have been published. The prevalence of congenital absent foot pulses varies in different studies and clearly depends on the character of the study. Robertson and colleagues examined 547 young healthy subjects by means of digital palpation and a Doppler probe and found the dorsal pedal artery (ADP) to be absent in 15 subjects (3%) bilaterally or unilaterally, with the posterior tibial artery (ATP) absent in only one person (Robertson et al. 1990). Yamada and colleagues found an absent ADP in 6.7%

cases of cadavers, ATP being present in all limbs (Yamada et al. 1993). In an earlier anatomic study, the absence of ATP was reported to be 2% (Adachi 1928).

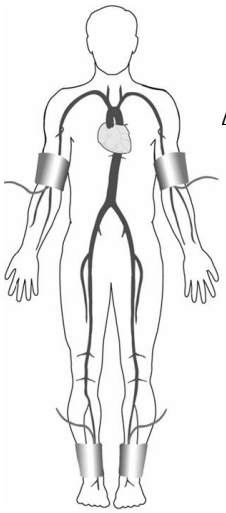
2.1.6.2 Non-invasive tests

Non-invasive assessment methods to confirm the diagnosis of PAD include ABI measurement, segmental limb pressures (SLP), pulse volume recordings (PVR) and stress tests. Additional methods, such as toe pressure and transcutaneous oxygen tension ($TcPO_2$) measurements, may also be required for selected patients. The latter has been used mainly in patients with CLI, specifically to evaluate the risk of subsequent amputation, but its value in addition to pressure measurements is questionable (Carter and Tate 2006).

Distal pressure measurements, including the ABI, have been employed to assess the haemodynamics of a vascular patient for several decades (Carter 1968, Yao et al. 1969, Baker and Dix 1981). For the ABI, brachial, posterior tibial and dorsalis pedis pressures are measured with a 10–12 cm sphygmomanometer cuff placed on the arms and above the ankles. A continuous-wave Doppler (CW Doppler) is then used to determine the systolic pressure in each artery as the flow resumes after cuff deflation. These pressures are normalized to the higher brachial pressure of either arm to form the ABI (Figure 4). ABI $\leq$ 0.9 is typically considered diagnostic for PAD (TASC working group 2007).

The location and extent of PAD can be further defined by measuring segmental pressures. Segmental limb pressures are obtained the same way as the ABI but at the level of the thigh and calf. The location of an occlusive lesion is obvious from the pressure gradient (> 20 mmHg) between different cuffs (Schmieder and Comerota 2001). Pulse volume recordings are performed by using pneumoplethysmografy: the cuff at the selected site is inflated to 60–65 mmHg, which is sufficient to detect volume changes without occluding the artery, and the pulse wave is registered. Both SLP and PVR provide a more objective assessment of the presence and location of PAD: both alone are 85% accurate in detecting significant stenosis compared to angiography, and when used together, a diagnostic accuracy of 97% has been reported (Rutherford et al. 1979, TASC working group 2007).

Stress tests are required when the patient is presenting with typical vascular claudication, but the limb appears to have normal arterial circulation on inspection and palpation, or ABI is only marginally abnormal. The treadmill exercise test combined with pre- and post-exercise pressure measurements is the most frequently applied method. In the usual test, the patient walks at 3.2 km per hour on a 12% grade for 12 minutes or until forced to stop due to the leg pain. Although a decrease of ABI by 15%–20% is typically considered diagnostic for PAD, expressing the ankle pressure change as a percentage of the absolute pre-exercise pressure has been shown to have the smallest variability (Amirhamzeh et al. 1997, TASC working group 2007).



$$ABI = \frac{\text{The higher of the ankle systolic pressures (posterior tibial or dorsalis pedis)}}{\text{Higher arm systolic pressure (left or right)}}$$

Figure 4. Measurement of the ankle-brachial index (ABI). (Modified from: TASC working group 2007).

2.1.6.2.1 Elevated ankle-brachial index

Ankle pressures and, consequently, ABI can be falsely elevated due to the use of a too narrow cuff or due to mediasclerosis, which complicates clinical decision-making and PAD diagnosis. In the case of cuff size, the problem can be avoided by using cuffs that are at least 120% of the diameter of the measuring site (Zierler and Sumner 2000, Mätzke 2004). Mediasclerosis is mainly caused by diabetes, end-stage renal disease and systemic corticosteroid treatment (Goss et al. 1989, McMillan 1997, Leskinen et al. 2002) and should be suspected if appropriately-sized cuffs are used but ABI still remains high.

The prevalence of elevated ABI varies significantly depending on the study design and threshold values used. While some authors have recommended that elevation of the ABI should be suspected when ABI exceeds 1.15, others have used the cut-off value between 1.3 and 1.5 (Goss et al. 1989, Takolander and Rauwerda 1996, Meijer et al. 1998, Leskinen et al. 2002, Begelman and Jaff 2006). In 1968 Carter found the incidence of lower extremity vessel incompressibility to be only 1% in a series of 600 limbs studied (Carter 1968). In more recent publications, the prevalence has ranged from less than 1% to up to 13.6%, and even higher among diabetic patients (Goss et al. 1989, Meijer et al. 1998, Diehm et al. 2004, Stein et al. 2006). The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) recommends the cut-off value of ABI > 1.4, while the American College of Cardiology and the American Heart Association (ACC/AHA) recommendations for elevated (noncompressible vessel) ABI is ≥ 1.3 (Hirsch et al. 2006, TASC working group 2007).

In the case of elevated ABI, as the toe vessels usually do not become non-compressible, the measurement of toe pressures and toe-brachial index (TBI) is recommended to diagnose possible PAD (Young et al. 1993, Mayfield et al.

1998, Zierler and Sumner 2000, Sahli et al. 2004). This is achieved by placing a small occlusion cuff proximally on the first or second toe with a flow sensor and measuring the arm pressures at the same time. Normal toe pressures run approximately 30 mmHg lower than ankle pressure and, consequently, TBI < 0.6 or < 0.7 is considered diagnostic for PAD (Raines 1993, TASC working group 2007). Absolute toe pressure of less than 30 mmHg usually implies that some form of intervention is required in order to save the limb (Second European Consensus Document on Chronic Critical leg ischemia 1991, TransAtlantic Inter-Society Consensus 2000).

Although widely recommended, the measurement of toe pressure has some limitations such as vasospasm and calcification of the small vessels, thus complicating the interpretation of the results (Sawka and Carter 1992, Brooks et al. 2001). Furthermore, the measurement of toe pressure is more time-consuming and technically difficult in addition to requiring additional equipment.

As patients with elevated ABI have often been excluded from studies on PAD, the clinical significance of this phenomenon remains unknown. To date, there is no data available on the possible relationship between elevated ABI and PAD. However, according to two recently published studies, the association between elevated ABI and total and cardiovascular mortality is similar to that of low ABI, suggesting that such a relationship exists (Resnick et al. 2004, O'Hare et al. 2006).

2.1.6.3 Imaging

Imaging is indicated for patients in whom the decision has been made to proceed with revascularization if a suitable lesion is demonstrated. For patients with CLI, imaging and revascularization are usually mandatory, whereas for patients with intermittent claudication, the decision is highly individual and should be considered not only in terms of the claudication distance but also in terms of the effect on the quality of life and self care (TASC working group 2007). The options currently available for imaging include angiography, duplex ultrasound, magnetic resonance angiography (MRA) and computed tomographic angiography (CTA).

Digital subtraction angiography (DSA), despite its invasive nature, is still considered the method of choice in most cases. Good quality DSA provides an excellent overall picture of the morphological changes in the vascular tree but does not provide any information regarding the haemodynamic state of the limb (Mätzke 2004). The most common complications related to angiography are reactions to contrast media and contrast-induced renal failure, in addition to puncture site complications such as haemorrhage and thrombosis (Sacks 2000). Furthermore, DSA carries a 0.16% mortality risk (TASC working group 2007).

Duplex ultrasound, MRA and CTA are non-invasive imaging methods and, therefore, attractive alternatives for angiography. Duplex ultrasound is useful in determining the location of disease and delineating between stenotic and occlusive lesions (Begelman and Jaff 2006). Its role as a preoperative tool is increasing, and it is recommended for surveillance of vein grafts despite the

conflicting results of published studies on its clinical utility (Luján et al. 2002, Hirsch et al. 2006). The limitations of duplex ultrasound include the variability of technical expertise and the duration of the examination (TASC working group 2007).

Both MRA and CTA techniques are widely adopted for the initial assessment and treatment planning of patients with PAD, and current data even obviates the need for conventional angiography (Koelemay et al. 2001, Kock et al. 2005). Magnetic resonance angiography is considered safe and rapid but has a tendency to overestimate the degree of stenosis (Begelman and Jaff 2006). Patient-related factors (patients with defibrillators, permanent pacemakers, spinal cord stimulators, and claustrophobia) may also restrict the use of this assessment modality. The limitations of CTA, on the other hand, include the use of an iodine-based contrast medium, considerable doses of ionizing radiation and the presence of calcium, which may complicate adequate evaluation.

2.2 Functional ability and the disablement process

Functional ability, or functioning, refers to the ability to perform basic tasks of everyday life (Satariano 2005, p. 125). These tasks range from individual generic tasks, such as walking, to more complicated activities associated with the performance of a social role – for example, employment. The capacity of the individuals on the one hand and the resources and demands of the social and physical environments on the other define the level and ease of functioning. As the measures of functional ability are based on ordinal, interval or continuous scales and physical performance measures rather than on dichotomous classification, functioning usually provides a more comprehensive and complete picture of health and well-being of an individual (Satariano 2005, p. 130). However, variation in the measurements of functional limitation restricts cross-study comparison and can lead to inconsistency in the results (Johnson and Wolinsky 1993, Boult et al. 1994). A universal language, such as the disablement model, with which to discuss functioning and disability is therefore needed.

There are two conceptual disablement frameworks that have received widespread attention and use in the research of the epidemiology of ageing and disability. The first is the disablement model developed by Nagi in 1976 and elaborated by Verbrugge and Jette in 1994 (Nagi 1976, Verbrugge and Jette 1994). The second is the current version of the International Classification of Impairments, Disabilities and Handicaps (ICIDH) (World Health Organization 1980) known as the International Classification of Functioning, Disability and Health (ICF) (World Health Organization 2001). Both of these frameworks represent the contemporary biopsychosocial view of the phenomenon of disability describing it as a consequence of biological, personal, environmental and social forces.

Nagi's disablement model, and the term disablement itself, has its origin in the early 1960s as a part of a study of disability and in his work on conceptual issues related to rehabilitation (Nagi 1964, Nagi 1965). He constructed a

framework that differentiated among four distinct, but related, phenomena: pathology, impairment, functional limitation and disability.

The first stage in the model, pathology, represents the presence of disease or injury. Active pathology – for example, peripheral arterial disease – results in the interruption of normal cellular process and simultaneous response of the organism to restore a normal state. The second stage, impairment, refers to a loss or abnormality at the organ (tissue) and body system level. The symptoms of active pathology are also classified in this stage. Lower extremity muscle weakness and balance deterioration can be understood as impairments due to PAD. Functional limitations represent restrictions in the ability to perform basic actions in daily living normally, such as walking. A common representation of PAD is intermittent claudication. The process can ultimately lead to disability, which reflects a physical or a mental limitation in a social context; disability is a product of the interaction of the individual with the environment. However, according to Nagi, not all impairments or functional limitations necessarily accelerate disability, and similar patterns of disability may result from different types of impairments and limitations in function (Nagi 1991).

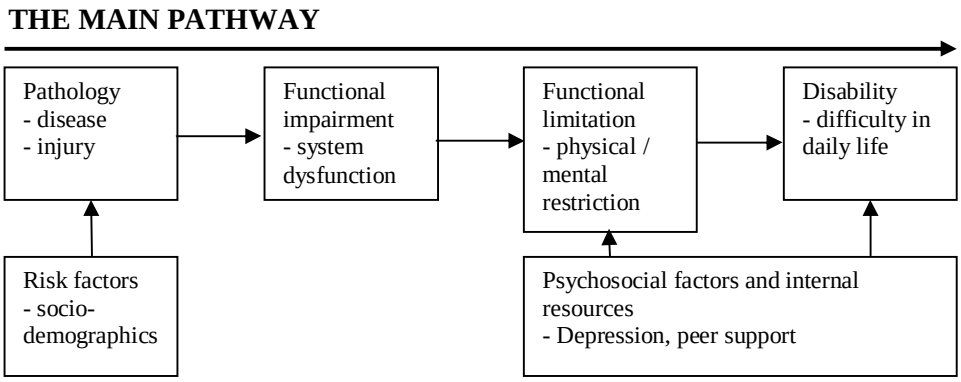


Figure 5. Conceptual model of the disablement process. (Modified from: Verbrugge and Jette 1994).

Verbrugge and Jette extended the Nagi disablement model by integrating the influences of social and cultural environment as well as personal factors (lifestyle behaviours and attitudes) within the framework, thus attempting to attain a full sociomedical framework of disablement (Figure 5) (Verbrugge and Jette 1994). They recognized that there are factors influencing the ongoing disablement process that are external to the main pathway and that one can interpret the whole process in relation to them. These factors, or variables, which modify the process of becoming disabled include: predisposing risk factors, intra-individual factors and extra-individual factors. Risk factors are predisposing phenomena that a person possesses prior to the onset of the disablement process, with lifestyle as an example. Intra-individual factors are

those within an individual, such as lifestyle and behavioural changes, following the onset of a disabling condition, whereas extra-individual factors operate outside a person. These can include medical care, medications, therapeutic regimens and accommodated physical and social environments.

The interrelations of the factors within the disablement process have been actively studied during the past decade, but where exactly they fit into the model and what types of effects they have in the disablement process have yet to be determined. Moreover, much of the research has focused on isolated components of the disablement process. For example, some studies have examined the relationship between chronic diseases and functional limitations, while others have studied the predictive value of these limitations in respect of future disability status (Boult et al. 1994, Guralnik et al. 1994, Guralnik et al. 1995, Ostir et al. 1998 Guralnik et al. 2000). One of the first studies to use the conceptual model of the disablement process as a guide for the analysis was the investigation by Lawrence and Jette in 1996 (Lawrence and Jette 1996). They found a causal ordering of the components, but the results were weakened by the fact that the authors did not include psychosocial factors and internal resources, i.e. factors that can impact the daily functioning of an individual, in the analysis.

The International Classification of Impairments, Disabilities and Handicaps (ICIDH) (World Health Organization 1980) was released in 1980. The model differentiated a series of three distinct concepts related to disease and health conditions – impairments, disabilities and handicaps – and it was to become part of the WHO family of international classifications. However, it failed to receive endorsement by the World Health Assembly and, therefore, its major revision, known as the International Classification of Functioning, Disability and Health (ICF) (World Health Organization 2001), was introduced in 2001 (Figure 6).

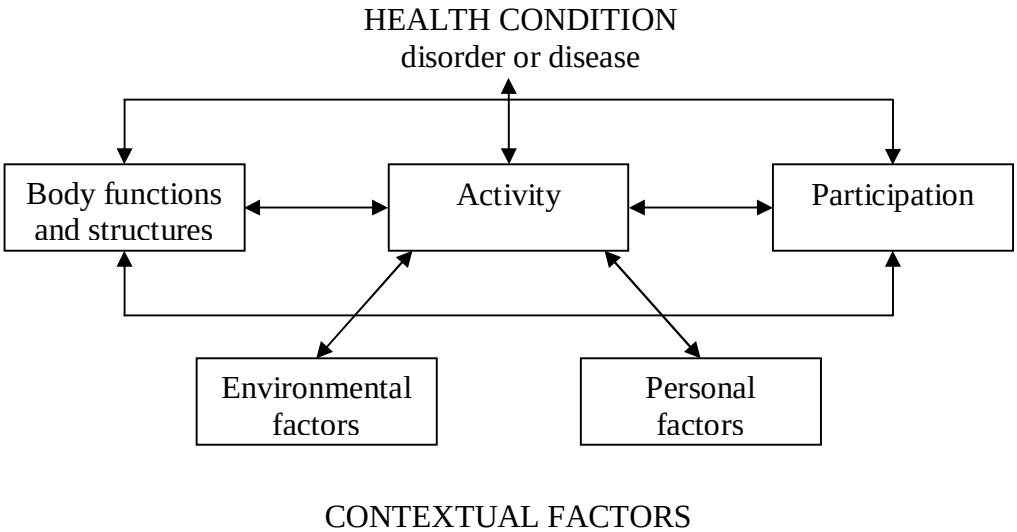


Figure 6. Classification of Functioning, Disability and Health (ICF). (Modified from: World Health Organization 2001).

Like Verbrugge and Jette's extension of Nagi's framework, the ICF model describes human function and decreases in functioning as the product of a dynamic interaction between various health conditions and contextual factors. The ICF identifies three levels of human function: functioning at the level of body parts, the whole person, and the whole person in his or her overall environment. All of these levels respectively contain three domains of human function: body functions and structures, activities and participation.

The main concepts included within the Nagi and the ICF models are remarkably similar, but the terms used to represent them are quite different. In the ICF model, the active pathology is replaced by the term health conditions, impairment by body functions and structures, functional limitation by activity/activity limitation, and disability by participation/participation restriction. The ICF further organizes the domains of activity and participation into subdomains, such as learning and applying knowledge, general tasks and demands, communication, self-care, etc., and these subdomains are the same for both models.

The disablement process is complex. The elaboration of Nagi's model and the development of the ICH framework are therefore welcome advances in the field of ageing and disability research. They have contributed significantly to a better understanding of the process of disablement, its physiological basis and the measurement of the key variables. ICH still has certain problem areas, such as the absence of clear and measurable domains and subdomains, which need to be solved before it can be adapted widely by researchers (Jette 2006).

2.2.1 Lower extremity function

The ability to walk and climb stairs without assistance, i.e. a person's mobility, reflects the functional status of the lower extremities and underlies a person's ability to function independently in the community (Patel et al. 2006). Mobility difficulties are common in older people and increase with age. They represent a critical stage in the disablement process as they predict disability, nursing home placement and mortality (Guralnik et al. 1994, Guralnik et al. 1995, Rantanen et al. 1999, Guralnik et al. 2000).

In addition to age, there are other demographic patterns and socioeconomic and environmental factors that can have negative impact on mobility but are constant or not easy to alter: female sex, non-white ethnic background, lower socioeconomic status, lower levels of psychological resources and living in an institutional residence are among the risk factors shown to correlate with higher levels of disability and greater dependence (Berkman et al. 1993, Seeman et al. 1994, Mendes de Leon et al. 1997, Fried and Guralnik 1997, Seeman et al. 1999). Therefore, as the global population is ageing, it is important to investigate modifiable factors that might help preserve mobility in later life. By changing health behaviours, such as smoking, alcohol consumption and diet, or by duly treating diseases and co-morbidities, the progression of disability can probably be delayed.

The deterioration of lower extremity function can develop gradually during a number of years, or the onset of mobility loss can be sudden, for example, after a stroke or hip fracture (Ferrucci et al. 1996). Ferrucci and co-authors demonstrated that in younger age groups, mobility loss is more likely to develop abruptly, whereas among those aged 85 and older, disability takes a more progressive course. These findings were later supported by Guralnik et al., as they found that over 80% of those aged 85 or older developed progressive disability (Guralnik et al. 2001). The corresponding figure for those under the age of 85 was 60%. Their study also showed that the risk factors and mortality outcomes are different for each type of mobility disability. Having three or more chronic conditions at the baseline was a powerful predictor of progressive disability, while stroke history, for example, predicted catastrophic mobility loss. The type of mobility loss among those who developed severe disability did not influence the survival during the first three years of the study, but beyond three years those with catastrophic disability had a relative risk of death of 0.4 (95% CI 0.2–0.9) compared with those with progressive disability.

Previous studies have shown that specific disease combinations may have a synergistic effect on progressive disability (Ettinger et al. 1994, Fried et al. 1999). This implies that successful prevention or treatment of one such condition may have a marked impact on reducing functional decline. By combining different treatment modalities with active rehabilitation, better results can be expected in the reduction of mobility loss (Guralnik et al. 2001).

2.2.2 Evaluation of lower extremity function

Walking and mobility can be assessed with self-reports and physical performance measures (Guralnik et al. 1989). Self-report measures are commonly used in epidemiologic studies, because they are easier in the context of large-scale, longitudinal studies of older adults. They typically ascertain the inability to perform, need for assistance and/or presence of difficulty or tiredness associated with a variety of functions such as climbing stairs, walking long distances, grasping and handling as well as lifting and carrying (Rosow and Breslau 1966, Nagi 1976). There are, however, concerns that a self-report of functioning is not sufficiently precise or physiologically meaningful. Therefore, physical performance methods were introduced to assess physical functioning in a more objective and precise way (Guralnik et al. 1989).

Physical performance measures were originally developed for clinical and laboratory-based studies, but they have been adapted for administration in a home setting as well, thus making them suitable for field-based epidemiologic studies. The level of performance is typically assessed in terms of whether the task can be completed and, more importantly, what was the quality of the performance. However, there are some concerns regarding the use of these measures: they may be more time-consuming, they may require adequate space and special equipment or training, and they may increase the possibility of injuries. Furthermore, the large variety of performance-based tests has sometimes made it hard to evaluate what is actually being measured (Satariano

2005, p.141). At the same time, physical performance measures have several strengths, including good face validity for the tasks being evaluated and greater reproducibility and sensitivity to change, in addition to the measures being less influenced by poor cognitive functioning, culture, language, education or physical environment (Guralnik et al. 1989). The measures of physical performance may also identify older persons with a preclinical stage of disability; i.e. to identify people who may develop frank disability unless preventive interventions are used (Fried et al. 2001).

In the following sections, the methods to evaluate lower extremity function are discussed in detail in the extent to which they were used in the current study based on the framework of Nagi's disablement model (Nagi 1976).

2.2.2.1 Postural balance

Postural control refers to the act of maintaining, achieving or restoring the line of gravity within the base of support (Pollock et al. 2000). Consequently, the ability to control postural balance is an important determinant of safe mobility, from basic activities of daily living to more demanding occupational duties and leisure activities. The control of posture is maintained by a complex sensorimotor system (Johansson and Magnusson 1991). As people grow old, one or more components of this intricate system can be affected, thus adversely impacting balance performance (Woollacott and Shumway-Cook 1990). Proposed mechanisms to explain balance deterioration in advanced age include vestibular dysfunction, reduction in somatosensation, changes in visual function, increased reaction time and muscle weakness (Lord and Ward 1994, Era et al. 1996, Whitney et al. 2000, Lord and Dayhew 2001).

The effect of age on postural balance has been demonstrated in a number of cross-sectional studies, and longitudinal data is also available (Hytönen et al. 1993, Gu et al. 1996, Hurley et al. 1998, Era et al. 2002). Some of the studies further suggest that there is a U-shape relationship between balance performance and age, indicating that children and the oldest adults sway most while trying to maintain a still stance (Hytönen et al. 1993). However, clear differences between age groups have only been found in studies with more difficult test conditions – for example, when using perturbations or altering sensory input by manipulating the visual feedback (Hurley et al. 1998, Choy et al. 2003). The question of sex-related differences in balance performance has also been investigated, but the results are conflicting (Overstall et al. 1977, Suomi and Koceja 1994, Era et al. 1996, Era et al. 2006).

Postural balance, and its integrity, is typically evaluated with tests of static or dynamic posturography (Johansson and Magnusson 1991). Static posturography, or postural steadiness, characterizes the performance of the postural control system in a static position and an environment with a series of standing positions with increasing difficulty; for example, with eyes open and eyes closed. One of the most commonly used field test is the standard standing balance battery introduced by Guralnik in 1994 (Guralnik et al. 1994). In a clinical setting, on

the other hand, functional balance tests with tasks related to daily living have gained popularity (Tinetti 1986, Berg et al. 1989).

During the past 20 years, stabilometry or static force plate measures of the centre of pressure (COP) have become increasingly popular (Woollacott 2000). Furthermore, the introduction of a computerized force platform has made it possible to measure balance quantitatively and to detect smaller differences or changes than would have been possible through tests of the categorized performance type, which often have ceiling and floor effects confounding the interpretation of the results (Era et al. 2006). The COP is the location of the vertical reaction vector of the surface of a force platform on which the subject stands, and it reflects the orientations of the body segments as well as the movements of the body to keep the centre of gravity over the base of support (Winter et al. 1990). The anterio-posterior (AP) and medio-lateral (ML) displacement of the COP can be measured with a force platform. It has been proposed that sway velocity rather than absolute sway is a more sensitive measure of balance problems; both AP and ML sway velocity measurements have been shown to be indicators of imbalance (Fernie et al. 1982, Maki et al. 1994, Era et al. 2006). Moreover, it has been suggested that increased ML sway in particular may be an indicator of the propensity to fall (Maki et al. 1994).

Despite their feasibility, measures of balance during a quiet stance may be insensitive to many balance problems. Therefore, researchers have begun to measure reactive balance function, or dynamic posturography, which measures the postural response to an applied or volitional postural perturbation on a moveable platform (Inglis et al. 1994, Brown et al. 1999).

2.2.2.2 Walking endurance and walking velocity

Walking tests have been recognized as a useful and reproducible measure of exercise tolerance and functional capacity, a prognostic marker for nursing home placement, as well as mortality (McGavin et al. 1976, Guyatt et al. 1985, Guralnik et al. 1994, Guralnik et al. 1995, Guralnik et al. 2000, Arslan et al. 2007). Among the first tests to measure walking endurance was the 12-minute walking test which was based on a 12-minute running test described by Cooper (Cooper 1968, McGavin et al. 1976). The 12-minute test, although highly reproducible, is time-consuming and exhausting for the participants. Therefore, Butland and co-authors introduced the 6-minute walking test, which was found to be efficient and less stressful for the participant, corresponding more closely to the usual day-to-day activity (Butland et al. 1982). Ever since its introduction, the 6-minute test has been used in clinical practice and trials worldwide, and it is usually performed as described by Guyatt in 1985 (Guyatt et al. 1985). The test is conducted in a long corridor, and the participant is instructed to walk from end to end, covering as much ground as they can during the allocated time.

The 6-minute walk, a test of walking endurance, has been found a useful measure of functional capacity and subsequent mortality in patients with chronic heart failure, and it has been shown to reflect the functional status of patients with lung disease (Guyatt et al. 1985, Sciurba et al. 2003, Arslan et al. 2007).

Kallinen and colleagues studied the predictive value of an exercise test with a bicycle ergometer for mortality in 282 community-dwelling elderly individuals and found that those who could not complete the test had an almost two-fold risk of death during a nine-year follow-up when compared to those who completed the test (Kallinen et al. 2006).

Walking velocity, or walking speed, is yet another parameter to characterize lower extremity function. The 8-foot (2.4 metres) walking test is used widely (Guralnik et al. 1994). The test is performed by instructing the participant to walk the course with his/her usual speed. The test is repeated twice, and the faster of the two is used for analyses. Lately, the 4-metre walking test has been utilized increasingly as it is expected to differentiate better than the 8-foot test (Guralnik et al. 1995, McDermott et al. 2002a, McDermott 2005a). In this test, individuals are asked to walk the distance with normal and maximal paces. As with the 8-foot test, both tests are repeated twice, and the fastest time is used in the analysis. Maximum speed tests provide an idea of the reserves the person has, whereas customary, or normal, walking speed is a function of the person's maximum speed.

In cross-sectional studies, both the usual-pace and fast-pace tests have been shown to correlate inversely with the level of disability in younger individuals, but it has been proposed that normal rather than maximal walking speed should be used to assess functional status among subjects over 75 years of age (Guralnik et al. 1994, Guralnik et al. 1995, Shinkai et al. 2000). Furthermore, slower walking speed has been demonstrated to be a predictor of subsequent disability in the elderly (Guralnik et al. 1995). In addition to the aforementioned tests, researches have also used other distances to measure gait speed; for example, 5 and 10-metre tests have commonly been used in post-stroke functional status evaluation (Collen et al. 1990, Salbach et al. 2001).

2.2.2.3 Perceived difficulty in mobility

There are a number of ways and scales to assess disability, none of which have thusfar received universal acceptance. Today, disability is often categorized as mobility disability, disability in basic activities of daily living (ADL) or disability in instrumental activities of daily living (IADL).

Problems in mobility are usually the first sign of disability, and they may vary from having difficulties only in highly challenging tasks to being bedridden. Mobility disability is often preceded by preclinical disability, which can usually be recognized by simply asking whether a person has changed the way of performing a mobility task because of a health or physical condition (Fried et al. 2001, Wolinsky et al. 2005, Weiss et al. 2007). Although performance tests of the lower extremities have been shown to predict mobility disability, objective walking speed and reported difficulty are not equivalent but rather measure different dimensions of the same phenomenon (Jylhä et al. 2001). Previous studies have shown that poor performance is not necessarily associated with disability and that the level of disability may also be greater than the observed limitation (Guralnik et al. 1995, Ferrer et al. 1999). These findings are in line

with Nagi's theory that not all impairments lead to functional impairment and not all functional limitations lead to disability (Nagi 1991).

The evaluation of ADL disabilities is highly important, as they represent more severe disability. Self-reported limitations in ADL for the purpose of assessing functional performance have been used in gerontological studies since the early 1960s (Katz et al. 1963). The ADL index of Katz assesses the extent to which the subject requires personal or technical assistance in basic self-care tasks. Although the Katz index was originally tested with hospitalized patients, the index, or its variations, is today commonly used to measure functional status in community-dwelling elderly individuals (Guralnik et al. 1994, Leinonen et al. 2006). ADL tasks typically include bathing, dressing, eating, going to the toilet, getting into or out of bed and moving indoors. In addition to being an important measure of the quality of life, ADL has also prognostic significance as it has been shown to associate with subsequent mortality and nursing home placement (Guralnik et al. 1994, Lee 2000). Regardless of the widespread use of the ADL index, the evidence of its reliability and validity is, however, limited (Reuben at al 1995, Brach et al. 2002).

IADL tests assess a person's physical and cognitive performances, i.e. the ease of adaptation to the environment (Satariano 2005, p 134). An IADL scale usually includes a broad variety of items from housekeeping and home maintenance to the use of medicine and financial management (Lawton and Brody 1969). According to the available literature, the development of IADL disability is associated with lower rather than upper extremity functional limitation (Jette et al. 1990). Furthermore, it seems that IADL disability develops earlier than ADL disability (Sonn 1996).

Owing to the diversity of performance tests and self-report items, it is often reasonable and advisable to combine both of these measures in order to characterize the functional status of an individual more thoroughly (Guralnik et al. 1994). This is rationalized as performance tests scores, contrary to self-reports, have been shown to distinguish a gradient of risk for mortality and nursing home placement among those who report almost no disability at baseline (Guralnik et al. 1994).

2.3 Functional decline in peripheral arterial disease

Although intermittent claudication as such may restrict an individual's ability to cope with the demands of everyday life, the relationship between PAD and functional decline, as described above, has attracted little attention until recently. Traditionally, treadmill testing has been used to assess walking capacity in patients with PAD, and only since the late 1990s has the causality of PAD and functional decline been studied systematically using specific questionnaires and objective measures (Hiatt et al. 1995, McDermott et al. 1998a, McDermott et al. 1998b, McDermott et al. 1999).

Today, sufficient data is available to confirm that PAD is not only cross-sectionally related to the degree of functional impairment but that it also predicts the degree of functional decline over time (McDermott et al. 2004a, McDermott

et al. 2006a, McDermott et al. 2007a). It is worth noticing, however, that even today this topic interests only a limited number of researchers, which became obvious during the review of the literature.

2.3.1 Functional impairment in PAD

The manifestations of functional impairment in PAD include nerve and muscle dysfunction of the lower extremities, as well as deterioration in balance (Gardner and Montgomery 2001, McDermott et al. 2004b, McDermott et al. 2004c, McDermott et al. 2006b, McDermott 2008). The number of studies addressing the problem of nerve dysfunction in PAD is limited, with conflicting results (Chopra and Hurwitz 1969, Weber and Ziegler 2002, Teunissen et al. 2002a, McDermott et al. 2004b, McDermott et al. 2004c). Chopra and Hurwitz studied nerve conduction in the peroneal and femoral nerves but found no difference between subjects with or without PAD, while Weber and Ziegler found impaired function in peroneal and tibial nerves among those with PAD. The main finding by Teunissen and colleagues as regards the lower extremity nerve function was that tibial nerve motor conduction velocity was significantly lower among patients with PAD compared to their counterparts. McDermott and co-authors have studied nerve function in PAD in significantly larger populations than the other aforementioned authors, and they have come to a conclusion that PAD is associated with reduced peroneal nerve conduction velocity. Despite the discrepancies in the results, there is some evidence that chronic ischaemia may serve as a pathophysiological pathway in peripheral polyneuropathy, as it has been shown to increase the basal lamina area thickness of the endoneural vessels and decrease perineural innervation of peripheral nerves (Teunissen et al. 2000, Teunissen et al. 2002b).

There is some evidence of the association between PAD and impaired leg muscle strength – this association has been shown to be present regardless of the symptoms; i.e. patients with only diminished ABI also suffer from reduced strength (Regensteiner et al. 1993a, Scott-Okafor et al. 2001, McDermott et al. 2004b, McDermott et al. 2004c, McDermott et al. 2008). Available data also shows that PAD is associated with increased muscle fibre deficiencies and reduced calf skeletal muscle area, which may mediate the relationship between PAD and functional decline (Farinon et al. 1984, Regensteiner et al. 1993a, McDermott et al. 2007a).

In line with the results regarding nerve dysfunction, the results on the association between lower extremity muscle strength and PAD are not consistent. This can be explained by the differences in study populations and the modalities that were used to measure muscle strength and power. Furthermore, no longitudinal data is available, and, therefore, definitive conclusions about the possible causal pathway of PAD, leg strength and functional decline cannot be made at this point.

Even though the relationship between PAD and balance impairment has not received much interest from researchers, the results of the existing literature indicate that individuals with PAD, symptomatic or asymptomatic, are prone to

balance disturbances (McDermott et al. 2000, McDermott et al. 2002a). Gardner and Montgomery have also proposed that patients with PAD have a greater likelihood of falling compared to their counterparts without PAD, but this finding was not supported in a recent study by Arseven and co-authors (Gardner and Montgomery 2001, Arseven et al. 2008). Standing balance in relation to PAD has mostly been assessed by categorized performance-type tests, which often have ceiling and floor effects confounding the results (Era et al. 2006). Furthermore, the results of the balance tests have usually been evaluated together with repeated chair rises and four-metre walking velocity as a part of the summary performance score, a measure that predicts mobility loss, nursing home placement and mortality among community-dwelling individuals (Guralnik et al. 1994, Guralnik et al. 1995, McDermott et al. 2001b). This and the fact that COP-based indicators or computerized force platforms have not been used to characterize postural steadiness may complicate the evaluation of the degree of balance deterioration in patients with PAD.

2.3.2 Functional limitation in PAD

According to the Nagi's disablement model, claudication can be considered a functional limitation due to PAD (Nagi 1965, Verbrugge and Jette 1994). In addition to typical Rose claudication, a patient may present with atypical symptoms, such as non-calf-claudication, or, more often, they can be asymptomatic (Hirch 2001, McDermott et al. 2000, Stoeffers 1996, Sigvant 2007). The character of leg symptoms can be determined with a specific questionnaire, the San Diego Claudication Questionnaire, which was introduced in 1996 and is now commonly used in the research on PAD and functional decline (Criqui et al. 1996, McDermott et al. 1999, McDermott et al. 2001). Functional limitation is perhaps the most widely studied field of functional decline in PAD; both cross-sectional and longitudinal data exist on the subject (McDermott et al. 1998a, McDermott et al. 1998b, McDermott et al. 2001a, McDermott et al. 2002b, McDermott et al. 2004a, McDermott et al. 2007b).

Six-minute walk and four-metre walking velocity are the two most often used tests to assess functional limitation in PAD. In their study on 158 patients with PAD, defined as ABI < 0.9, and 70 controls, McDermott and colleagues found that ABI levels were independently associated with walking endurance and walking velocity: the lower the ABI, the shorter the distance walked and the slower the walking speed (McDermott et al. 1998b). They further concluded that as walking velocity has important prognostic implications for functioning, ABI may be used to identify patients at risk of mobility loss. In a further study by the same authors, functional limitation was assessed in 460 men and women with PAD divided into six groups according to the legs symptoms (modified San Diego claudication questionnaire); the results were compared with 130 controls (McDermott et al. 2001a). All groups with PAD demonstrated poorer walking endurance and walking velocity than those without PAD. The results also suggested that the severity of functional limitation depends on the character of the symptoms: those with rest pain and those who reported walking less than six

blocks (without exertional leg pain) had the worst results. This finding implicates that not only the severity of ischaemia but other factors such as co-morbid diseases and physical activity may also alter PAD-associated leg symptoms.

As a part of the Women's Health and Aging Study, McDermott and co-writers studied the association between baseline ABI and functional decline over time in 847 women (McDermott et al. 2002b). They showed that low ABI (<0.6) at baseline is associated with significantly greater decline in walking speed over three years when compared with normal ABI (0.9–1.5). In a consecutive study by the same author, the association was investigated among 676 individuals, 417 with and 259 without PAD over two years – the results were further analyzed in regard to leg symptoms (McDermott et al. 2004a). Lower baseline ABI values were found to be associated with greater annual decline in walking endurance but not in walking velocity. According to the results, the nature of leg symptoms also predicts the degree of functional decline, as individuals with more severe symptoms showed greater decline in six-minute walking and walking speed. The association between female sex and greater functional decline among patients with PAD has been demonstrated in one study, but the results could not be repeated in a subsequent paper (McDermott et al. 2003a, McDermott et al. 2005a). In a recent study, poorer baseline functional performance was shown to explain the greater decline in functional performance over time in persons with PAD (McDermott et al. 2007b).

The walking impairment questionnaire (WIQ, Table 3) was originally designed to assess treatment effects on claudication-limited walking ability, and the WIQ scores are shown to respond to exercise training and revascularisation in patients with symptomatic PAD (Regenstainer et al. 1990, Regensteiner et al. 1993b, Hiatt et al. 1995, Regensteiner et al. 1996). As the WIQ measures walking endurance, walking speed and stair-climbing ability in the community, it has also been used alone or together with objective assessing methods to describe functional impairment in individuals with PAD (McDermott et al. 1999, Gardner and Montgomery 2001). Available data suggest that the WIQ is a valid method to estimate the walking ability in PAD with or without intermittent claudication (McDermott et al. 1998a, Izquierdo-Porrera et al. 2005, Myers et al. 2008).

2.3.3 Disability in PAD

Vogt and colleagues were among the first to show that PAD causes disability, measured as difficulties in performing activities of daily living (Vogt et al. 1994). The study was conducted among 1,492 community-dwelling women aged 65 years or older. Women with PAD, defined as an ABI ≤ 0.9, were more likely to report difficulties in one or more daily activities than their counterparts without PAD. However, after adjusting for age and other potential confounders, only a difficulty in walking 2–3 blocks remained significantly associated with PAD. In a recent study by Brach and colleagues, lower baseline ABI was shown to associate with an increased risk of mobility disability and ADL disability over a period of six years (Brach et al. 2008).

Most of the existing literature has used the WIQ questionnaire or QoL questionnaires to assess functional limitation and disability in PAD (Myers et al. 2008). Generic QoL questionnaires, such as The Medical Outcomes Survey SF-36 (MOS-SF 36), include domains that assess mobility and PADL disability (Ware and Sherbourne 1992). When used alongside with disease-specific questionnaires, they provide information that can be compared with other patient populations or existing norms (Liles et al. 2006). Disease-specific questionnaires, on the other hand, are mainly used as a means of pre- and post-intervention measurement, but they also give the patient an opportunity to describe his or her health situation more profoundly, thus giving the physician a more extensive picture of the patient's current status (de Vries et al. 2005).

The role of symptomatic PAD, namely IC, in reducing QoL and with an impact on activities of daily living has been demonstrated in several studies (Khaira et al. 1996, Breek et al. 2001, Breek et al. 2002, de Vries 2005). The comparison of the results is, however, troublesome, as a different QoL questionnaire was used in each study. Furthermore, in a study by Long and colleagues, QoL was found to correlate more closely with the symptoms of PAD rather than with ABI (Long et al. 2004). In addition to decreased QoL associated with physical performance, PAD, regardless of the symptoms, increases the risk of emotional and social impairments (McDermott et al. 2003b).

Table 3. The Walking Impairment Questionnaire (WIQ). (Modified from : Regenstainer et al. 1990)

	Degree of difficulty				
Walking distance*	**None**	**Slight**	**some**	**Much**	**Unable**
Walking indoors	4	3	2	1	0
Walking 50 feet	4	3	2	1	0
Walking 150 feet	4	3	2	1	0
Walking 300 feet	4	3	2	1	0
Walking 600 feet	4	3	2	1	0
Walking 900 feet	4	3	2	1	0
Walking 1500 feet	4	3	2	1	0
Walking speed*					
Walking 1 block slowly	4	3	2	1	0
Walking 1 block at an average speed	4	3	2	1	0
Walking 1 block quickly	4	3	2	1	0
Running or jogging 1 block	4	3	2	1	0
Stair climbing*					
Climbing 1 flight of stairs	4	3	2	1	0
Climbing 2 flights of stairs	4	3	2	1	0
Climbing 3 flights of stairs	4	3	2	1	0

* Report the degree of physical difficulty that best describes how hard it was for you to perform the individual tasks without stopping to rest during last week.

3 AIMS OF THE STUDY

The aim of the present study was to investigate factors underlying or indicating PAD in older people and to describe functional decline in peripheral arterial disease (Figure 7). The specific study questions were:

1. Does elevated ABI indicate PAD in older people referred to a vascular outpatient clinic?

2. How common is PAD in a population-based sample of nonagenarians?

3. How does PAD correlate with balance and mobility in older people?

4. Does PAD predict mortality in nonagenarians?

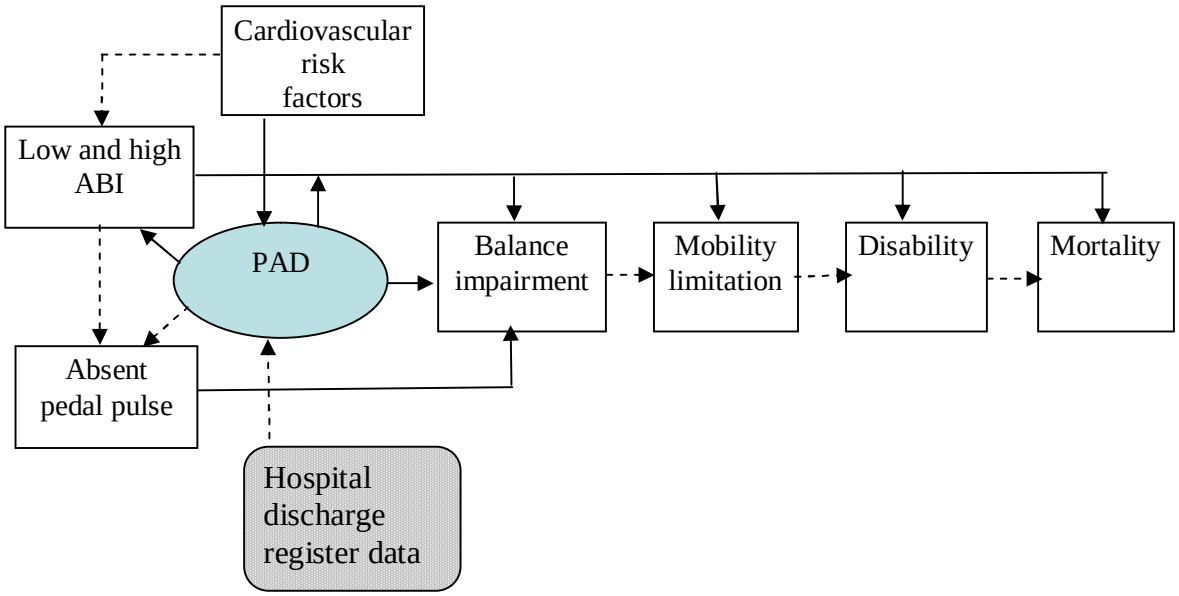


Figure 7. Analytical framework of the current study.

4 MATERIAL AND METHODS

4.1 Subjects and study designs

4.1.1 Clinical population (I)

The study population consisted of consecutive patients referred to the vascular outpatient clinic at Tampere University Hospital (TAUH) between April 2002 and January 2006. TAUH serves a region with roughly 470,000 inhabitants, and all vascular surgical consultations, diagnostics and procedures are carried out exclusively at TAUH. Every patient visit to the hospital is recorded in the central register with the diagnosis and reason for attendance.

Patients with suspected lower extremity arterial insufficiency were included in the study. The measurement of the ABI and the TBI was attempted for all new admissions (N=2,237) during the study period. The pressure measurements were unsuccessful for 51 patients (2.3%). Patients with successful measurements and with no prior lower extremity vascular procedures (N=1,762, 78.8%) were subjected to further analysis.

4.1.2 The Evergreen project (II, III)

The Evergreen project is a population-based prospective study on the health of elderly residents in the city of Jyväskylä (Heikkinen 1998). In 1989, the entire 75-year-old population (N=380) and the entire 80-year-old (N=283) population of 1990 were targeted. At the baseline, 92% of the 75-year-old individuals took part in home interviews and 78% participated in laboratory measurements at the study centre. The figures for the 80-year-old participants were 90% and 72%, respectively. Follow-up studies were conducted at five and at ten years, and for the 75-year group at 15 years.

The target group for Study II consisted of all the 90-year-old residents (N=79) who at the beginning of the project in 1989, at the age of 75, were living in the community. The study was conducted between 1 November and 31 December 2004. Twenty-one eligible candidates declined or were unable to participate. Therefore, 58 (73 %) individuals formed the study group. Participants were interviewed and examined at the research centre, at home or in hospital or some other long-term care facility. The original Evergreen study protocol was followed with the addition of ABI measurement. The participants were followed until the end of December 2005, at which point information on death was obtained from the patients' case records at Jyväskylä Central Hospital.

For Study III we chose participants from the 75-year-old and the 80-year-old cohorts who at baseline had pedal pulse status recorded and had participated in at least one balance test out of the maximum three. A total of 419 individuals (137 men and 282 women) met the inclusion criteria, and 220 subjects attended the 5-year follow-up. Of the remaining 217 individuals, 135 had died, and a further 64 were either only interviewed at home, had refused to participate further in the study or were unable to perform any of the balance tests. At ten years, 248 of the

initial 419 participants had died and 78 dropped out. Therefore, 93 individuals formed the 10-year follow-up group.

4.1.3 The Health 2000 survey (IV)

The Health 2000 survey was conducted by the National Public Health Institute (KTL) between August 2000 and June 2001 (Aromaa and Koskinen 2004). The two-stage stratified cluster sampling design was planned by Statistics Finland. The sampling frame consisted of adults aged 30 years and over in mainland Finland. The frame was stratified according to the regions surrounding the five university hospitals. From each region, 16 hospital districts were further sampled as clusters. Eighty hospital districts therefore comprised the primary sampling units. The initial sample comprised 8,028 individuals, 87% of whom were interviewed and 79% took part in the health examination.

The target group for this study was defined as those aged 65 years or older (N=2194). A total of 1,490 (68%) individuals participated in a comprehensive health examination at one of the research centres. Of these initial 1,490 individuals, at least one balance test on a force platform was performed by 1,323 (60%) participants; 167 (11%) did not perform any of the balance tests, mostly due to technical problems with the force platform system. Patients who declined to participate in the study, or who were interviewed or examined at home, were not included in the study.

4.2 ABI and TBI measurement; Definition of PAD

In the first study, ABI and TBI were measured using the Nicolet VasoGuard (Nicolet Vascular Inc, Madison, WI), a device that allows simultaneous systolic blood pressure measurements from the upper and lower extremities by means of photoplethysmography. The measurements were carried out by trained vascular nurses. Photoplethysmographic probes were attached to the tips of the big toes, and cuffs were placed on the arms and legs above the ankle or at the base of the big toes. The higher of the two simultaneously measured brachial systolic blood pressure values was used in the analysis. As a rule, values obtained from single ABI or TBI measurements were used, but no pathological or near-pathological values were accepted unless they could be repeated.

An ankle-brachial index less or equal to 0.9 was considered low, ABI > 0.9 or < 1.3 normal and ABI ≥ 1.3 elevated. Patients with an ABI ≤0.9 and/or TBI < 0.60 in either leg were regarded as presenting with PAD. Patients with an ABI ≥ 1.3 in both legs or in one leg, in which case the other side had to be normal, were categorized as belonging to the elevated ABI group. Furthermore, for 69 patients with an elevated ankle brachial index, DSA had been performed after the initial consultation. In one patient the TBI was > 0.60, while the rest had a TBI < 0.60, i.e. PAD. The angiography images were reviewed for the presence of PAD, defined as a more than 50% narrowing of the arterial lumen in any arterial segment of the lower extremities.

The presence of PAD in Study II was evaluated by measuring systolic blood pressure at both brachial arteries, the dorsal pedal artery and the posterior tibial artery in both the left and right leg using an 8-MHz CW-Doppler probe (Handydop, Kranzbüler, Germany) and a manual sphygmomanometer. For each artery a single blood pressure reading was taken with the subject in a supine position after 10 minutes' rest. Systolic and diastolic blood pressure in both arms was also measured. The ratio of the highest systolic blood pressure value obtained for each leg to the highest value for the arm was calculated. Peripheral arterial disease was defined as an ABI of less than 0.9 in either leg. An ABI above 0.9 and below 1.4 was considered normal, while an ABI greater than 1.4 was defined as elevated.

In the Health 2000 survey (Study IV), the presence of PAD was elicited by the question, "Has a doctor diagnosed arterial stenosis in the lower extremities?" Further information was obtained about hospitalization (National Hospital Discharge Register) due to PAD from the Research and Development Centre for Welfare and Health (STAKES) using the appropriate ICD 8–10 codes (4402, I70.2). Participants with a solely self-reported diagnosis were classified as having "possible PAD" and those with related hospitalization as having "confirmed PAD". In Study IV, depending on the presence of possible or confirmed PAD and diabetes, four groups were formed: individuals with PAD and diabetes (PAD+DM), individuals with PAD (PAD), individuals with diabetes (DM) and individuals without PAD and diabetes (NORMAL).

4.3 Pulse palpation

The baseline physical examination of all Evergreen project participants was carried out by the same experienced physician. The palpation findings for femoral and dorsal pedal arteries (ADP) were recorded in the study protocol as either present or absent. For Study III, subjects were divided into three groups according to the findings: both ADP pulses present, one ADP pulse absent and both ADP pulses absent.

4.4 PAD risk factors

PAD risk factors, as well as the presence of CHD or CVD, were ascertained during the clinical examination according to the appropriate Evergreen (Heikkinen 1998) and Health 2000 study protocols (Aromaa and Koskinen 2004) (Studies II–IV), or at the outpatient clinic at TAUH (Study I), and they were defined as a self-reported physician's diagnosis or medication use for the condition. Additional criteria included the following: diabetes was established as non-fasting blood glucose $\geq$ 11.0 mmol/l (Study II) and fasting glucose $\geq$ 6.1 mmol/l (Study IV); hypercholesterolemia was defined as a total cholesterol level higher than 6.45 mmol/l in Study II and higher than 6.5 mmol/l in Study IV, while the total cholesterol/HDL ratio > 5.0 was regarded as unfavourable in Study III; systolic blood pressure $\geq$ 160 mmHg or diastolic blood pressure $\geq$ 95 mmHg was considered diagnostic for hypertension in Studies II and IV.

4.5 Balance tests

Balance measurements were carried out in Studies III and IV using force platforms. These systems record movement of the centre of pressure while the person is standing. The person is instructed to stand as still as possible during the test, and large numbers are therefore considered to indicate poor postural control. In Study III, a piezoelectric force platform (Kistler 9861 A) with an area of 600 mm x 1200 mm was used. The piezoelectric transducers located in each corner of the platform registered the vertical and antero-posterior as well as medio-lateral horizontal forces independently of each other. The signals were amplified (Kistler amplifier) and stored by a multi-channel analogue recorder (Racal 7). In Study IV, balance was measured using the Good Balance measurement system (Metitur Ltd., Jyväskylä, Finland). The system consists of an equilateral triangular force platform connected to a computer through a 3-channel amplifier with an A/D-converter and a computer programme.

In Study III, three different tests were performed while the subjects were standing on the platform: 1) normal standing for 40 seconds with eyes open (EO), hands placed on hips, feet comfortably apart and gaze fixed on a mark at eye level; 2) normal standing as before for 40 seconds, but with eyes closed (EC); 3) tandem standing (feet positioned heel-to-toe along the midline of the platform) for 20 seconds. The tests were performed in the same order for every subject, starting with the easiest test and proceeding to the more difficult ones. For each test, three balance outcome variables were calculated: antero-posterior sway velocity, medio-lateral sway velocity and velocity moment. Sway velocity characterizes the displacement of the centre of pressure during each second of the test. Velocity moment refers to the first moment of velocity calculated as the mean area covered by the movement of the centre of force during each second of the test, taking into account both the distance from the geometrical midpoint of the test and the speed of movement during the same period.

In Study IV, the participants were asked to perform four different tests: 1) normal standing for 30 seconds with eyes open (EO), feet comfortably apart, arms in a relaxed position in front of the body with one hand gripping the wrist of the opposite arm, and gaze fixed on a mark at eye level (distance 2 metres); 2) normal standing as before for 30 seconds, but with eyes closed (EC); 3) semi-tandem standing (the first metatarsal joint of one foot besides the calcaneus of the other foot) with eyes open for 20 seconds with the arms hanging freely at the sides so that they could be used for balance correction if necessary; and, finally, 4) tandem standing (feet positioned heel to toe along the midline of the platform) with eyes open for 20 seconds and arms positioned as in the semi-tandem test. The tandem test was performed only if the participant was able to hold the semi-tandem position for 10 seconds. The tests were performed in the same order for every subject, starting with the easiest test and proceeding to the more difficult ones. If the subject was not able to perform the test (e.g., the eyes were opened before the end of the second test or the position of the feet changed during the semi-tandem or tandem test), he/she was allowed another try at the same test. For

each test, two balance outcome variables were analysed: AP and ML sway velocity.

4.6 Lower extremity functional status

In Study IV, lower extremity functional status was evaluated with the aid of two performance tests and self-reports. Those who were bedridden and reported severe difficulty in moving indoors, moving outdoors or negotiating stairs were categorized as having severe mobility limitation. In a subgroup of 36 participants, lower extremity functional status was further studied by performing walking endurance and walking velocity tests. To assess walking endurance, subjects walked for 6 minutes. If necessary, subjects were allowed to rest during the test. The distance achieved at the end of 6 minutes was recorded. Walking velocity was assessed by walking a 10-metre distance at maximal pace. The walk was performed once and the time recorded. Walking velocity was calculated by dividing 10 by the recorded time.

Basic characteristics of each study are summarized in Table 4.

4.7 Statistical analyses

The analyses were conducted using SPSS software for Windows, versions 11.5–15.0 (SPSS, Chicago, IL, USA). For Study IV, version 14.0 with Complex Samples, which takes the sampling design into account, was employed. For discrete variables, analyses were made with the aid of cross-tabulations combined with the chi-square-test; comparisons of means between two groups were carried out with the t-test for independent samples, and, between three groups, with One-Way ANOVA. A general linear model was used to determine possible interactions as well as the relationship between PAD and postural balance. The effects of time and pulse status on balance were assessed by one-way ANOVA for repeated measures. Logistic regression analysis was applied to calculate the likelihood of PAD among those with elevated ABI (Study I), the likelihood of a person not being able to perform the most demanding balance tests (Studies III–IV) and the risk of mortality among nonagenarians with an abnormal ABI (Study II). The models were adjusted for age, sex and other confounding factors when appropriate. A P-value < 0.05 was considered statistically significant.

Table 4. Basic characteristics of the individual studies.

Study	I	II	III	IV
Number of participants	1,762	58	419	1,323
Males	1,041	11	137	567
Females	721	47	282	756
Design	retrospective clinical study	population-based prospective study	population-based prospective study	population-based cross-sectional study
Predictors	elevated ABI	PAD	absent pedal pulses	PAD
Outcomes	prevalence of elevated ABI PAD risk factors among those with elevated ABI	prevalence of PAD among nonagenarians mobility, disability and mortality	impaired balance	impaired balance
Definition of PAD	ABI and TBI measurement by means of photoplethysmography	ABI measurement with CW-Doppler and manual sphygmomanometer	absent pedal pulses	self-report National Hospital Discharge Register
Evaluation of impairment / functional limitation	–	walking endurance walking velocity self-reports of difficulty	balance tests on force platform	balance tests on force platform

5 RESULTS

5.1 The prevalence of elevated ABI, and its association with PAD

Among the individuals referred to a vascular outpatient clinic, elevated ABI was detected in 148 (8.4%) patients; 1,139 (64.6%) had a low ABI and 475 (27.0%) a normal ABI. The distribution was not dependent on sex. The prevalence of low ABI, i.e. PAD, increased steadily with the age of the patients, while the prevalence of high ABI was not dependent on age (Figure 8). The prevalence of cardiovascular risk factors and other co-morbid conditions as well as systemic corticosteroid treatment between the ABI categories is presented in Table 5.

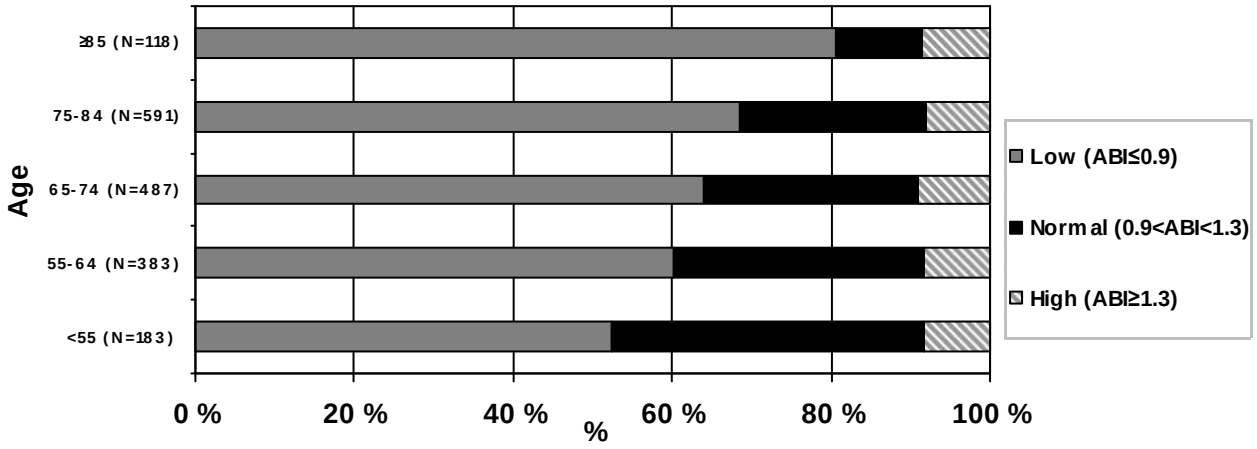


Figure 8. The distribution of the ABI categories according to age.

Of the 148 patients presenting with an elevated ABI, 92 (62.2%) were consequently considered to have PAD according to the TBI measurement. Evaluation of the DSA images confirmed the diagnosis in all 68 available cases. A non-significant increase in the prevalence of PAD was observed in the older age groups (60% among those below the age of 55 years and 80% among those over 85 years of age, p=0.741). Peripheral arterial disease was significantly more prevalent among subjects with severe symptoms (rest pain, ulcer, gangrene) than among those referred due to intermittent claudication (83.8% and 45.3%, respectively, p<0.001).

According to the logistic regression model, there was a more than ten-fold risk of being diagnosed with PAD among patients with chronic renal failure, five-fold risk among those with a history of smoking and a more than three-fold risk among those with CHD (Table 6). The presence of hyperlipidaemia seemed to have a protective effect against PAD (OR 0.3, p=0.022). However, 22 (84.6%) of the 26 patients with hyperlipidaemia were receiving statin treatment.

Table 5. The distribution of cardiovascular risk factors and co-morbid conditions according to ABI level (N=1762).

Measure	ABI≤0.9	0.9<ABI<1.3	ABI≥1.3	p-value*
	N=1139 (%)	N=475 (%)	N=148 (%)	
Diabetes mellitus	380 (33)	147 (31)	73 (49)	<0.001
Hyperlipidaemia	318 (28)	129 (27)	26 (18)	0.028
Hypertension	604 (53)	210 (44)	64 (43)	0.001
Smoking	374 (33)	76 (16)	15 (10)	<0.001
CHD	397 (35)	134 (28)	57 (39)	0.014
Cerebrovascular disease	122 (11)	43 (9)	12 (8)	0.429
Respiratory disease	140 (12)	36 (8)	18 (12)	0.020
Renal failure	67 (6)	29 (6)	21 (14)	0.001
Systemic corticosteroid treatment	39 (3)	19 (4)	20 (14)	<0.001

* χ^2- test

Table 6. The odds of being diagnosed with PAD among those with elevated ABI (N=148). Logistic regression model.

Measure	OR	95%CI
Diabetes	1.66	0.76-3.63
Hyperlipidaemia	0.30	0.11-0.84
Hypertension	0.72	0.33-1.57
Smoking	5.63	1.22-26.00
CHD	3.44	1.46-8.12
Cerebrovascular disease	1.32	0.34-5.17
Respiratory disease	1.47	0.46-4.70
Renal failure	10.31	2.07-51.30
Systemic corticosteroid treatment	1.87	0.55-6.30
Sex (male)	1.77	0.75-4.22
Age (per 10 years)	1.26	0.89-1.80

As 56 patients with an elevated ABI did not have PAD according to the TBI measurements, we further assessed the validity of different elevated ABI levels (1.3, 1.4 and 1.5) in identifying PAD. The prevalence of PAD was 78.2% (79/101) among subjects with an ABI > 1.4 and 83.5% (76/91) among those with an ABI > 1.5. Of the 475 patients with normal ABI, 118 (24.8%) had a TBI < 0.6. By pooling the normal and elevated ABI groups, i.e. all subjects with an ABI > 0.9 (N=623), and then defining the number of patients in the combined groups who had a TBI < 0.6 (N=210), we were able to determine the respective specificities and sensitivities. The specificities were good, with a tendency to

increase with the elevation of the threshold level (86%, 94% and 96%, respectively), whereas the sensitivities were only satisfactory (44%, 38% and 36%, respectively).

5.2 The prevalence of PAD in a population-based sample of nonagenarians

The prevalence of PAD among nonagenarians was 22% (13/58). With the exception of one person with a previous femoral amputation due to gangrene in the foot, all the cases detected were new. One person reported intermittent claudication during the interview, and the overall prevalence of asymptomatic disease was thus 85%. Fifteen (26%) participants had an ABI >1.4. One person with elevated ABI was on corticosteroid therapy, three had diabetes and none had end-stage renal disease (ESRD).

Of the total population, 35 (60%) had at least one manifestation of cardiovascular disease. The differences in the prevalence of individual risk factors between the ABI categories were not statistically significant. However, the accumulation of risk factors among those with an ABI<0.9 was significantly higher compared to the other two groups (p=0.03). Almost half (6/13; 46%) of the candidates with an ABI<0.9 were not using any antithrombotic agent. Three of these six individuals also suffered from other cardiovascular diseases. A total of nine individuals had a total cholesterol level over 6. 45 mmol/l. Four of them were on lipid-lowering therapy. Hypertension was present in ten candidates, five of whom were being treated with antihypertensive agents. All diabetics were receiving medication.

5.3 The relationship between PAD, balance and mobility in older people

In Study III, 266 of the initial 419 participants at baseline had normal pulse status, i.e., both ADP pulses were palpable; 42 subjects were lacking one and 111 both ADP pulses. The prevalence of coronary heart disease was significantly higher in the group with both ADP pulses absent (45.0%) when compared to the group with normal ADP pulses (32.3%) or one absent pulse (28.6%) (p=0.039). The distribution of PAD risk factors (male sex, smoking, hypertension, diabetes, unfavourable lipid status and obesity) and CVD among the groups was equal.

Data on 1,323 participants were available for the analysis in Study IV. The mean age was 74.5±7.0 years. A total of 45 subjects had been hospitalized due to PAD (3.4%). An additional 32 (2.4%) participants reported that they had been diagnosed with the disease, but no record of hospitalization was found for them. Of those with a confirmed diagnosis, 41 (91%) were currently suffering from claudication, while for those with a self-reported physician's diagnosis, the corresponding figure was 16 (50%). Table 7 summarizes the distribution of PAD risk factors and other chronic diseases according PAD status. A significant accumulation of PAD risk factors was observed among patients with a confirmed diagnosis.

Table 7. The distribution of PAD risk factors and other chronic diseases according to PAD status (N=1323).

Measure	Confirmed PAD (N=45) N (%)*	Possible PAD (N=32) N (%)*	PAD not present (N=1246) N (%)*	p-value
Age (Mean±SD)	75.1±6.9	73.3±5.9	73.9±6.7	0.411
Male sex	26(64)	19(51)	522(40)	0.013
Smoking				<0.001
current	9(22)	4(13)	111(10)	
previous	18(46)	14(44)	321(27)	
non-smoker	17(32)	14(44)	811(64)	
Diabetes	31(70)	12(37)	370(29)	<0.001
Hypertension	29(66)	18(54)	773(62)	0.754
Hyperlipidaemia	11(24)	9(29)	447(36)	0.200
Coronary heart disease	14(34)	9(27)	251(20)	0.104
Cerebrovascular disease	7(13)	4(12)	111(9)	0.295
COPD	1(8)	3(3)	47(3)	<0.001
Congestive heart failure	12(26)	9(28)	153(11)	0.001
Number of risk factors (Mean±SD, max 5)	2.8±1.1	2.3±1.1	2.0±1.1	<0.001

* Numbers are un - weighted, percentages weighted values

5.3.1 PAD and balance

The correlation between pedal pulse status and balance was analyzed both cross-sectionally and longitudinally. Results of the cross-sectional analysis of the association between balance test results and the ADP pulse status is presented in Table 8. Individuals with both ADP pulses absent had the worst recordings in the balance tests, while statistical significance was reached only in the normal standing eyes-open position (p=0.047) in AP sway. The interaction term for pulse status and age/sex did not reach statistical significance.

Table 9 presents the results of the balance tests between the three groups according to the certainty of PAD diagnosis. Participants with a confirmed PAD swayed significantly more than those with a possible diagnosis or those without PAD in all tests. The COP movement between the four groups according to the presence of PAD and diabetes is shown in Figure 9. Only the first two tests were analyzed as the number of individuals who could perform the third test with semi-tandem standing was too low for statistical calculations. The interaction term for diabetes and PAD did not reach statistical significance.

Table 8. Comparison of balance parameters in normal standing eyes open (EO) and eyes closed (EC) according to pulse status (mean±SD).

Parameter	Normal	Missing one ADP	Missing both ADP	p-value* for trend
Normal standing EO	N=263	N=39	N=109	
Antero-posterior velocity, mm/s	21.16±6.70	21.27±6.21	23.19±8.30	0.047
Medio-lateral velocity, mm/s	12.15±3.53	12.85±4.09	12.94±5.24	0.191
Velocity moment, mm²/s	44.46±23.68	46.23±21.27	47.73±30.76	0.522
Normal standing EC	N=260	N=41	N=109	
Antero-posterior velocity, mm/s	29.08±10.28	27.30±7.30	31.21±13.53	0.088
Medio-lateral velocity, mm/s	15.35±5.26	15.05±4.95	16.56± 9.73	0.251
Velocity moment, mm²/s	71.06±44.48	64.66±33.92	84.09±92.76	0.100

* One-way ANOVA

Table 9. Cross-sectional analysis of COP movement in normal standing eyes open (EO) and eyes closed (EC) and in semi-tandem positions (mean±SD; adjusted for age, sex, smoking, diabetes, COPD, congestive heart failure, and number of risk factors). General linear model.

Parameter	Confirmed PAD	Possible PAD	PAD not present	p-value
Normal standing EO	N=45	N=32	N=1246	
Antero-posterior velocity, mm/s	11.96±6.43	9.85±3.70	8.70±3.70	0.003
Medio-lateral velocity, mm/s	7.09±4.00	5.60±2.38	5.02±2.50	0.004
Normal standing EC	N=45	N=32	N=1208	
Antero-posterior velocity, mm/s	23.86±16.00	16.96±6.31	14.84±7.70	0.002
Medio-lateral velocity, mm/s	12.24±10.09	8.12±3.94	7.04±4.18	0.007
Semi-tandem	N=31	N=32	N=1031	
Antero-posterior velocity, mm/s	20.61±8.37	18.18±10.78	16.39±7.31	0.032
Medio-lateral velocity, mm/s	25.48±10.90	21.27± 8.72	19.67±8.92	0.010

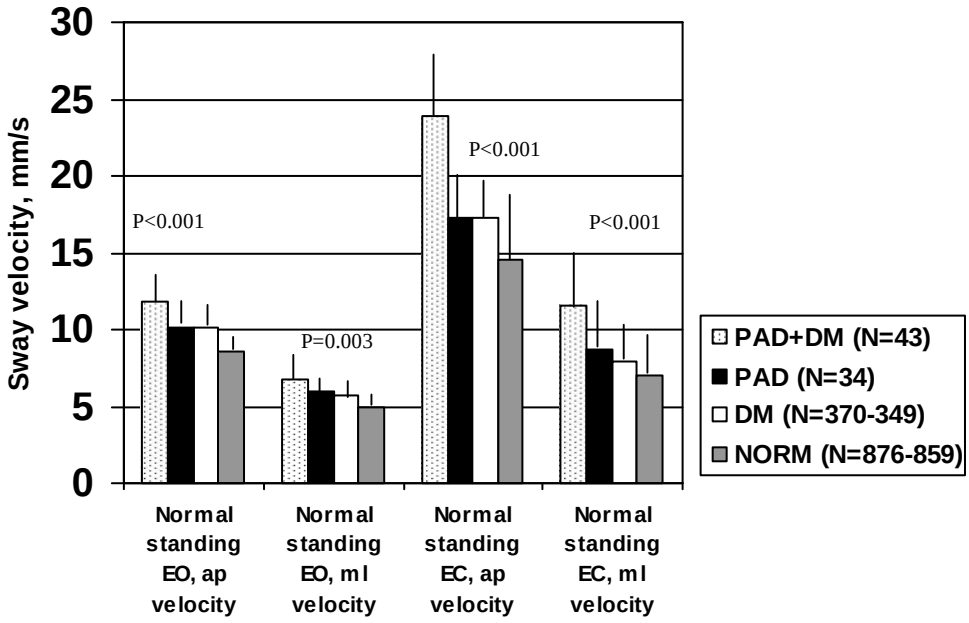
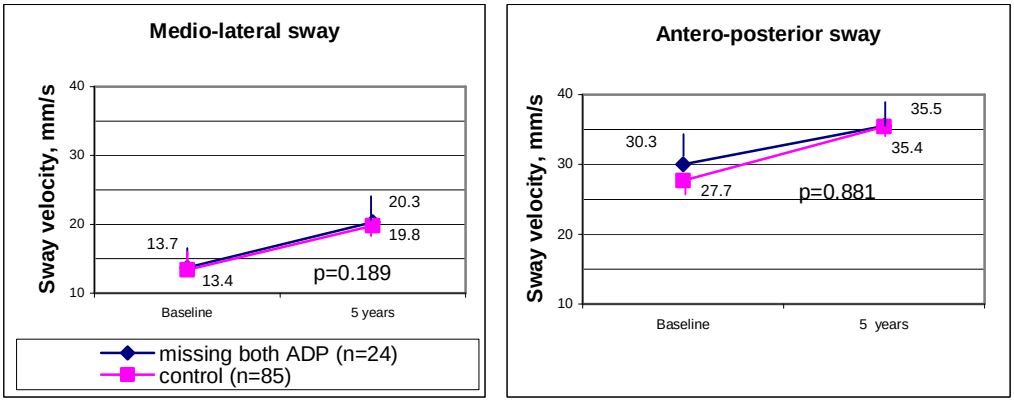


Figure 9. COP movement according to the presence of PAD and diabetes (Mean±SE; adjusted for age, sex, smoking, COPD, congestive heart failure and number of risk factors). General linear model.

The prospective analysis of changes in balance in Study III was carried out separately for those attending only the 5-year follow-up (n=109) and for those attending both the five and 10-year follow-ups (n=93). As the results of the balance measurements were similar for individuals with normal and one absent ADP pulse in the cross-sectional analysis, we combined these two groups for the longitudinal analysis reference and compared their results with the results of those lacking both ADP pulses.

Balance deterioration over time ($p<0.001$ for time) was observed for the five-year follow-up without statistically significant group-by-time interaction. At ten years' follow-up, the group-by-time interaction term was significant for the normal standing eyes-closed position. Persons with absent ADP pulses showed poorer results in both antero-posterior and medio-lateral sway ($p=0.025$ and 0.026, respectively). No systematic interaction between sex and pulse status was observed. Figure 10 shows the overall changes in balance over time in the normal standing eyes-closed position. The sex distribution was equal across the ADP status groups, with men accounting for approximately one third in each group at five and at ten years. The groups were also similar in terms of age. Absence of both ADP pulses did not predict a person's ability to attend the follow-up at either five or ten years (OR=1.54, 95%CI 0.98–2.40 and 1.40, 95%CI 0.85–2.40, respectively, for persons lacking both ADP pulses). No association with death during the ten-year follow-up was observed.

A



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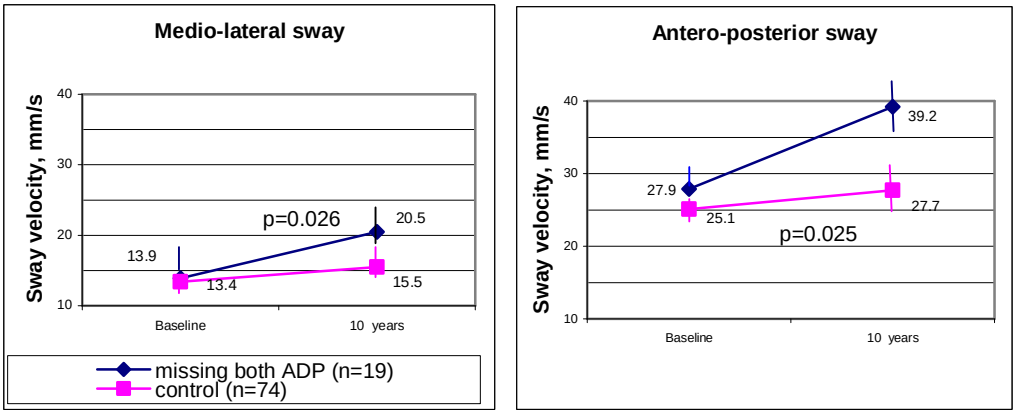

Figure 10. Changes in balance over time according to pulse status (normal standing EC position, mean±SE): A, at five years; B, at ten years (p=group by time interaction).

The effect of PAD on balance was further analysed by calculating the risk for not being able to perform the most demanding balance test in both studies. In Study III, 88 participants were unable to perform the most demanding test with full tandem standing. The number of non-performers was significantly higher among those with both ADP pulses missing than among those with one absent pulse or normal pulse status (29% vs. 17% vs. 16%, respectively, p=0.012). The odds ratio for persons with both ADP pulses missing for not being able to hold the tandem stance for 20 seconds was twofold (OR=2.20, 95%CI 1.29–3.78) compared to those with normal pulse status.

In Study IV, 572 (43%) participants were unable to perform the most challenging balance test (tandem standing). A more than three-fold risk for not being able to perform the most challenging test was observed among the subjects who had been hospitalized for PAD (OR=3.20, 95%CI 1.09–9.37) and an almost one-and-a-half-fold risk (OR=1.44, 95%CI 1.07–1.93) among those with diabetes, when compared to those without these diseases (Table 10).

Table 10. The odds for not being able to perform the tandem-standing test among those with PAD or diabetes alone or both of these diseases as compared to people without these diseases. Logistic regression model.

Measure	OR	95%CI
	Unadjusted analyses	
Confirmed PAD	2.64	1.04-6.85
Possible PAD	1.12	0.50-2.53
DM	1.59	1.25-2.03
PAD*+ diabetes	1.67	0.57-4.88
	Partially adjusted analyses **	
Confirmed PAD	2.76	1.05-7.21
Possible PAD	1.06	0.46-2.45
DM	1.59	1.24-2.05
PAD*+ diabetes	1.92	0.65-5.70
	Fully adjusted analyses #	
Confirmed PAD	3.20	1.09-9.37
Possible PAD	1.17	0.47-2.95
DM	1.44	1.07-1.93
PAD*+ diabetes	2.28	0.69-7.53

* Confirmed + possible cases
** adjusted for sex, smoking, COPD and congestive heart failure
# adjusted for age, sex, hypertension, hyperlipidaemia, coronary heart disease, cerebrovascular disease, COPD and congestive heart failure

5.3.2 PAD and mobility

The effects of PAD on mobility were studied among nonagenarians. Table 11 shows the proportions of people reporting severe difficulties in performing specific mobility tasks at different ABI levels. In three cases the results of self-reported difficulty were not available. Of the remaining 55 individuals, five were bedridden patients – two with normal ABI, two with an ABI > 1.4 and one with an ABI < 0.9. In general, people with low or high ABI reported more difficulties than those with normal ABI, but the results did not reach statistical significance. Combining low and high ABI into one group increased the statistical power, and the difference in difficulties in moving indoors became statistically significant (p=0.02).

Of the 36 individuals examined at the research centre, 23 (64 %) completed the six-minute walking test. The mean walking endurance for persons with a normal ABI (N=18) was 360±64 metres, while those who presented with an abnormal ABI (either < 0.9 or > 1.4, N=5) walked 298±66 metres (p=0.07). All except one participant took part in the ten-metre walking test. Maximal walking velocity for those with a normal ABI was 1.17±0.40 m/s, for those with low ABI 1.03±0.27 m/s, and for those with high ABI 1.04±0.15 m/s (p=0.51).

Of the twenty-one eligible 90-year-old candidates who declined or were unable to participate in the study, fourteen (5 men, 9 women) were interviewed. Eight of them were living at home, the rest in various long-term care facilities. Their self-rated health was, in general, satisfactory.

Table 11. Proportion of people reporting severe difficulties in performing different mobility tasks depending on ABI level (N=55).

PADL task	ABI < 0.9 N=13 (%)	0.9 ≤ ABI < 1.4 N=29 (%)	ABI > 1.4 N=13 (%)	p-value*
Moving indoors	6 (46)	5 (17)	6 (46)	0.07
Moving outdoors	7 (54)	9 (30)	7 (58)	0.23
Negotiating stairs	7 (54)	8 (28)	6 (46)	0.21
Any mobility task	7 (54)	11 (38)	8 (62)	0.32

* χ^2- test

5.4 The relationship between PAD and mortality among nonagenarians

A total of nine of the 58 (16%) participants died during the one-year follow-up; 2 (7%) with a normal ABI, 3 (23%) with an ABI<0.9 and 4 (27%) with an ABI>1.4 (p=0.115). When individuals with an abnormal ABI (either<0.9 or >1.4) were combined into one group, the difference in total mortality became significant compared to those with a normal ABI (25% vs. 7%, p=0.05). Six of the deaths were cardiovascular, one of which occurred with a normal ABI and five with an abnormal ABI (p=0.07).

6 DISCUSSION

This study examined the clinical features and consequences of PAD in older people. The main findings were that the prevalence of elevated ABI among patients admitted to vascular outpatient clinic was 8.4% and that of PAD among them 62%–84%, depending on the cut-off value (1.3, 1.4, 1.5). People with PAD had poorer postural control than those who did not have PAD, and even among nonagenarians abnormal ABI correlated with poorer mobility and increased mortality risk.

The topic of the current study is relevant from a scientific and clinical point of view. First of all, PAD is common in older people, with an overall prevalence of 3%–18%, increasing to 25%–30% in persons aged over 75 years (Stoffers et al. 1996, Meijer et al. 1998, Hirsch et al. 2001, Aronow et al. 2002, Diehm et al. 2004, Heidrich et al. 2004, Selvin and Earlinger 2004, Ostchega et al. 2007, Sigvant et al. 2007). According to the studies on the subject, the prevalence steadily increases from age 50 onwards and peaks at age 85 and over. Secondly, only a limited number of studies have been published which have addressed the consequences of PAD on physiological impairments and functional limitations (Hiatt et al. 1995, McDermott et al. 1998a, McDermott et al. 1998b, McDermott et al. 1999, McDermott et al. 2006a, McDermott et al. 2007a). Thirdly, very little is known about the morbidity and functional limitations among nonagenarians, an age group increasing rapidly with the ageing population (von Staruss et al. 2000, Goebeler et al. 2003).

According to Nagi's disablement model, active pathology results in the interruption of normal cellular processes which, if not prevented or treated properly, can lead to functional impairment and limitations; and eventually to disability (Nagi 1964, Nagi 1965, Nagi 1976). In old age, practically all people have chronic diseases, and therefore preventing their disabling processes is a priority. Furthermore, previous studies have shown that disease combinations may have a synergistic effect on the progression of disability (Ettinger et al. 1994, Fried et al. 1999). It is necessary to find ways to maintain functional independence for people with chronic conditions as well as to learn about what impact specific diseases have on body functions.

6.1 Diagnosis and prevalence of PAD

The diagnosis of PAD should be based on complete medical history, a physical examination and objective testing. Current recommendations suggest that in most cases objective assessment methods, including the ABI measurement, are mandatory and should be offered to 1) all individuals with exertional leg symptoms, 2) all patients aged 50–69 with cardiovascular risk factors, 3) all patients aged ≥ 70 years regardless of risk factor status, and 4) all patients with a Framingham risk score 10%–20% (Hirsch et al. 2006, TASC working group 2007). A number of factors may disturb the ABI measurement, thus complicating clinical decision-making and PAD diagnosis. These factors include

mediasclerosis, calcification of the media, which makes the crural arteries incompressible and results in a falsely elevated ABI.

The results of the current study for those referred to a vascular consultation concur with previous reports suggesting that the prevalence of elevated ABI ranges from less than 1% to up to 13.6%, and even higher among diabetic patients (Goss et al. 1989, Meijer et al. 1998, Diehm et al. 2004, Stein et al. 2006). Findings for nonagenarians, on the other hand, differ from these figures, as the prevalence ranged between 26% and 34% depending on the cutt-off level. Earlier data indicates that the prevalence of elevated ABI is affected by age, but this observation is not supported by the present findings with patients referred to the vascular outpatient clinic (Mayfield et al. 1998, Begelman and Jaff 2006). As patients with an elevated ABI have often been excluded from studies on PAD, the clinical significance of this phenomenon has remained unknown – to date, no previous data describes the possible relationship between elevated ABI and PAD.

Depending on the threshold value, the prevalence of PAD among those with an elevated ABI ranged between 62%–83% in the current study. Moreover, the results suggested that PAD should be suspected among patients with high ABI combined with chronic renal failure, a history of smoking, CHD and severe lower extremity symptoms. Since TBI measurement is often available only in specialized vascular units, these findings may guide clinicians as to when to suspect PAD among patients with an elevated ABI. If vascular surgical consultation is, for any reason, not required, the aforementioned findings should be taken into consideration when planning risk factor management for the particular patient.

Even though the clinical importance of high ABI is not as clear as low ABI, an association between high ABI and total and cardiovascular mortality similar to that of low ABI was found in two recently published studies (Resnick et al. 2004, O'Hare et al. 2006). The results of another publication further suggest that there is an association between elevated ABI and walking impairment (Allison et al. 2008). Since no objective method for diagnosing PAD among those with elevated ABI was used, the authors of the last-mentioned study conclude that the mechanism underlying this observation is obscure. As all previously mentioned studies have used a cut-off value of 1.4 to define elevated ABI, and as almost 80% of those with an ABI>1.4 had PAD in the present study, current results may partly explain why these associations exist.

The prevalence and clinical features of PAD in nonagenarians has not been studied in detail. Current data suggests that the prevalence of PAD among nonagenarians is approximately 20%. This, however, is propably an underestimation, as over a quarter of the study population had elevated ABI, which, as shown, is usually associated with PAD. Whatever the correct figure may be, the results in the present study are supported by previous observations suggesting that the overall prevalence of PAD in the highest age groups (65–85 years) is in the range of 20% to 50% and even higher, depending on the study design (Meijer et al. 1998, Hirsch et al. 2001, Diehm et al. 2004, Heidrich et al. 2004).

The overall prevalence of cardiovascular diseases among nonagenarians is not clear, but according to the limited literature available on the subject, the ranges fall between 42% and 78% (von Strauss et al. 2000, Goebeler et al. 2003). These figures agree with the current finding of 60%. Contrary to what has been stated earlier about the increasing incidence of IC and CLI with increasing age, our results suggest that PAD is mainly asymptomatic among nonagenarians (Murabito et al. 1997, Sigvant et al. 2007). At least two facts could explain this observation. Firstly, variations in understanding the question about the severity of problems in walking may have resulted in inaccurate responses. Secondly, the desire and need of a nonagenarian to walk at home or in the community can be so limited that normal activities do not cause any lower extremity symptoms (TASC working group 2007).

Current literature, including our results, suggests that clinicians should consider the potential clinical significance of the entire range of ABI values when evaluating a patient for PAD. Moreover, as most of the patients with PAD are asymptomatic, ABI measurement should become a routine in primary care and be offered to all elderly patients regardless of their age. From a scientific point of view, however, the inconsistency in the results regarding elevated ABI remains and the clinical utility of the ABI cannot be fully applied until a uniform cut-off value for elevated ABI, with sound scientific evidence, is available.

6.2 PAD, balance and mobility

The rationale behind studying the association between PAD, balance impairment and mobility difficulties is to be able to offer the patients timely secondary preventative measures and rehabilitation in order to avoid subsequent disability and nursing home placement. The available evidence, as shown below, seems to imply that an association exists, and functional performance measures and analysis of daily activities should therefore become a part of the clinical assessment of patients with PAD – and among older people in general. These measures are reliable and can be administered in the office setting (Guralnik et al. 1994, Guralnik et al. 1995, Suutama et al. 1999). However, systemic checks rather than one-time measurements are recommended in order to identify people most at risk – and to commence rehabilitation as early as possible.

6.2.1 Balance impairment

The present results suggest that peripheral arterial disease is associated with impaired balance in older people both cross-sectionally and longitudinally. In addition to poorer results in the actual balance tests, individuals with PAD seem to be at a greater risk of not being able to perform the most demanding balance tests.

The relationship between PAD and balance impairment has not been studied to any significant degree. The results of the existing literature indicate that individuals with PAD are prone to balance disturbances (McDermott et al. 2000, McDermott et al. 2002a). Gardner and Montgomery have also proposed

that patients with PAD have a greater likelihood of falling than their counterparts without PAD, but this finding was not supported in a recent study by Arseven and co-authors (Gardner and Montgomery 2001, Arseven et al. 2008). Standing balance in relation to PAD has mostly been assessed by categorized performance-type tests, which often have ceiling and floor effects confounding the results (Era et al. 2006). Our study is among the first to describe the relationship between decreased peripheral circulation and postural balance using COP-based indicators together with a computerized force platform – and our results are in line with earlier findings. The fact that individuals with severe PAD were at a more than three-fold risk of not being able to preform the most demanding balance test further emphasizes the relationship.

Diabetes is among the main risk factors for PAD, and it has become increasingly common in individuals with PAD (McDermott et al. 2001b, Diehm et al. 2004). As both PAD and diabetes have been shown to cause balance impairment, the problem was assessed here as well (Simmons et al. 1997, McDermott et al. 2000). According to our results, the presence of diabetes further worsened the deterioration in balance but alone affected balance somewhat less than PAD. These findings are similar to those of Dolan and co-authors, as they found PAD patients with diabetes to have poorer lower extremity function, including balance, than those with PAD alone (Dolan et al. 2002). According to the authors, the difference in function was probably due to diabetes-related neuropathy and cardiovascular disease. In the present study, self-reported information about the presence of diabetic neuropathy was available only for 178 (43%) out of 413 cases and was therefore not analyzed separately.

Despite the discrepancies in the results, there is some evidence that chronic ischaemia may serve as a pathophysiological pathway in peripheral polyneuropathy and impaired leg muscle strength (Regensteiner et al. 1993a, Teunissen et al. 2000, Scott-Okafor et al. 2001, Teunissen et al. 2002b, McDermott et al. 2004b, McDermott et al. 2004c, McDermott et al. 2008). Both muscle weakness and peripheral neuropathy, on the other hand, are proposed explanations to the poorer function of the postural control system in the elderly (Era et al. 1996, McDermott et al. 2006b). This causality, with a gradual evolvement of PAD together with ischaemic polyneuropathy, could explain the current findings of the longitudinal analysis. More importantly, the association became significant in the more challenging normal standing eyes-closed position, where balance is increasingly dependent on information from the proprioceptive and mechano-receptive organs.

6.2.2 Mobility and disability

The oldest old are the most rapidly growing subset of the elderly in the western societies (World Health Organization Report 1998). This increase is a result of improved living conditions, better preventive measures and medication as well as rehabilitation of chronic diseases (Kalache 1996). However, the knowledge about the functional status of nonagenarians is still limited. According to the

current literature, over 50% of them are independent and up to 80% require little or no assistance in their daily activities; the literature suggests that dementia is the main cause of disability among nonagenarians (von Staruss et al. 2000, Goebeler et al. 2003).

Our intention was to characterize functional limitation and disability among nonagenarians with and without PAD in a population-based sample. Unfortunately, as only 36 individuals participated in the walking tests, definitive conclusions cannot be drawn as regards the relationship between PAD and functional decline. However, the self-reports on specific mobility tasks suggest that a certain correlation exists. People with low or high ABI reported more difficulties in mobility than those with normal ABI, but the results did not reach statistical significance. When the low and high ABI groups were combined, these associations became more pronounced, and for moving indoors statistically significant ($p=0.02$). This observation perhaps reflects the overall activity level of a nonagenarian with a limited need to walk outdoors or climb stairs, thus making these questions irrelevant for some individuals. Nevertheless, our results imply that defining ABI could perhaps be used for nonagenarians to identify individuals at higher risk for mobility loss.

Although commonly used to determine functional status in the elderly since the early 1960s, ADL measurements have rarely been applied to assess the relationship between ABI level and lower extremity function (Katz et al. 1963, Laukkanen et al. 1997). The study by Vogt and colleagues seems to be among the few to show that PAD causes disability, measured as difficulties in performing activities of daily living (Vogt et al. 1994). In their recent paper, Brach and colleagues showed that lower baseline ABI is associated with increased risk of mobility disability and ADL disability over a period of six years (Brach et al. 2008). They also demonstrated that cardiovascular comorbidity partly explains the effect of a low ABI on disability. This finding underlines the importance of cardiovascular risk factor management in preventing disability among those with PAD.

Most studies related to this issue have explored the relationship between PAD, functional performance measures and/or QoL (McDermott et al. 1998, McDermott et al. 2002b, McDermott et al. 2004a, Myers et al. 2008). According to the results, PAD or low ABI is related to the decline in physical function both cross-sectionally and longitudinally. The role of symptomatic PAD, namely IC, in reducing QoL and with an impact on activities of daily living has also been shown in several studies (Khaira et al. 1996, Breek et al. 2001, Breek et al. 2002, de Vries 2005). However, sufficient data is still not available to describe the full extent to which PAD can impair a person's life (Liles et al. 2006).

6.3 PAD and mortality in nonagenarians

In 2004, the life expectancy of 90-year-olds in Finland was more than four years (Statistics Finland 2005: Population projection by age group). Despite the longevity, existing data indicates that nonagenarians are not exceptionally healthy, and that they have the same distribution of chronic disease as the main

population (DeRijke et al. 2000, Goebeler et al. 2003). Autopsy studies on nonagenarians and centenarians show that cardiovascular diseases are the most common cause of death among them (John and Koelmeyer 2001, Berzlanovich et al. 2005). This finding is supported by the present study, as 67% of the deaths were cardiovascular. Moreover, a significantly higher mortality was observed among those with an abnormal ABI over a one-year follow-up. Consequently, PAD does not seem to vanish after the age of 85, but rather continues to realize its natural history even among the oldest old.

Although cardiovascular diseases seem to be common among nonagenarians, the question of secondary prevention of atherosclerosis among them is controversial and has received little attention by researchers. At the same time, polypharmacy among very old people is common and involves increased risks of combined effects or unexpected side-effects (Beers 1997, Hanlon 1997 et al., Fick et al. 2003, Fialova et al. 2005, Simon et al. 2005). Therefore, it is important that drugs are prescribed with great caution for the very oldest individuals. However, nonagenarians should not be denied secondary prevention just because of their high age.

6.4 Methodological considerations

Except for the study on elevated ABI, the material used for the current analyses came from two large, completed, population-based studies (The Evergreen project, The Health 2000 survey). This research frame has a drawback as it forces the researchers to operate on ready-made instruments that cannot be altered. On the other hand, population-based studies usually come with a substantial number of participants, which allows not only reliable cross-sectional but also longitudinal evaluation of the problem in question. The retrospective design used in the study on elevated ABI has its own pitfalls as it involves possible data issues associated with the use of hospital discharge histories and patient case records.

The fact that an objective method for diagnosing PAD was not available in two of the studies is a disadvantage. Conflicting views have been expressed concerning the validity of pulse palpation in the process of diagnosing PAD, and the finding of absent pedal pulses possibly tends to over-diagnose PAD (Criqui et al. 1985, Christensen et al. 1989, Boyko et 1997, Stoffers et al. 1997, Khan et al. 2006, Collins 2006, Cournot et al. 2007). However, distal pressures and the palpability of an artery have been shown to correlate with each other, thus linking an absent pedal pulse with PAD (Brearley et al. 1992). The validity of the National Hospital Discharge Register has been shown to be good with reference to coronary heart disease and stroke (Leppälä et al. 1999, Pajunen et al. 2005). Therefore, the number of individuals with a confirmed, i.e. more severe, PAD diagnosis can be considered reliable as well. The agreement between self-reported diagnosis of PAD and medical records is considered moderate (Heckbert et al. 2004). Therefore, using the acquired information in the present study is not completely unjustified. The method used here to measure balance has been increasingly popular in recent studies, and both AP and ML sway

velocity measurements have been shown to be sensitive indicators of imbalance (Maki et al. 1994, Era et al. 2006). Good test-retest reproducibility of the standing balance tests has previously been reported and the method has also demonstrated good validity (Birmingham 2000, Sihvonen et al. 2004, Era et al. 2006). Moreover, it has been suggested that force platform data can be used as an indicator of the propensity to fall (Pajala et al. 2008).

The small sample size of the study on nonagenarians is a prominent limitation. Considering the participation rate of 73%, which is good for a target population of such a high age, we believe our results may be generalized to other similar populations. Other potential issues concerning the participation and generalization of the results are that the required information of only about 50% of those targeted in the Health 2000 material was available for the analysis, in addition to the loss of subjects to the follow-up in the Evergreen project resulting from studying an elderly sample over a long period. Among non-participants there may well be a great number of persons with severe chronic diseases, including PAD. A nationally representative study sample of the Health 2000 survey, however, allows generalizations, to an extent, on the national level. Furthermore, selective mortality in the Evergreen study population most probably caused the current findings to be underestimates rather than overestimates of the effects.

Despite the mentioned limitations in definitions and study designs, it is notable that the results concerning the relationship between PAD and functional decline are parallel and consistent. The use of analogous statistical methods and the avoidance of any statistical analyses whenever faced with an insufficient number of participant make our results more reliable. We have been able not only to support previous results but also produce novel information which deepens our understanding of PAD in general, and especially with regard to functional decline.

6.5 Future directions

Current data suggests that elevated ABI is associated with higher levels of cardiovascular morbidity and mortality similarly to low ABI (Resnick et al. 2004, O'Hare et al. 2006). In addition, higher levels of cardiovascular risk factors as well as coronary artery calcification have been shown to associate with an ABI above 1.30 (McDermott et al. 2005b, Allison et al. 2006). Further studies are needed to confirm these findings and to establish the role of elevated ABI as a potent risk factor for future cardiovascular events. More studies are also required to clarify the association between elevated ABI and PAD in order to recognize those not only at risk of cardiovascular death but also those who could benefit from revascularization to avoid possible amputation.

Supervised exercise programmes have been shown to be beneficial for patients with intermittent elucidation, as they improve exercise performance and community-based walking ability, but current knowledge is insufficient to accurately explain the potential mechanisms of this positive effect (Gardner and Poehlman 1995, Stewart et al. 2002). There is also evidence supporting the idea

that specifically targeted balance training programmes result in improvements in postural balance and that progressive resistance training improves muscle strength among older adults (Fiatarone et al. 1994, Rose and Clark 2000, Sihvonen et al. 2004, Binder et al. 2005). Therefore, further investigation should explore the possible added benefits, and their mechanisms, of post-operative balance and endurance-strength training after vascular procedures.

7 CONCLUSIONS

1) The prevalence of PAD among people at an advanced age with elevated ABI is 62%–84% depending on the cut-off value (1.3–1.5). PAD is significantly more probable among those with chronic renal failure, a history of smoking, CHD and severe lower extremity symptoms. The overall prevalence of elevated ABI among those referred to a vascular consultation is 8.4%.

2) The prevalence of PAD among nonagenarians is 22%, with a mainly asymptomatic clinical picture. The prevalence of elevated ABI among them is approximately 30%.

3) PAD is associated with poorer balance performance both cross-sectionally and longitudinally. The presence of diabetes seems to exacerbate the deterioration in balance but alone affects balance somewhat less than PAD. Nonagenarians with an abnormal ABI tend to report more difficulties in performing specific mobility tasks than those with a normal ABI.

4) An abnormal ABI is related to poorer 1-year survival in nonagenarians.

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Prevalence and Risk Factors of PAD among Patients with Elevated ABI

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Objectives. *To assess the prevalence and clinical significance of elevated ankle-brachial index (ABI) in patients referred to vascular consultation.*
Design. *Retrospective clinical study.*
Material and methods. *In 1,762 patients referred with a suspicion of peripheral arterial disease (PAD), ABI and toe brachial index (TBI) were measured by photoplethysmography. ABI ≥ 1.3 was considered falsely elevated and TBI < 0.60 was the diagnostic criterion for PAD.*
Results. *The prevalence of elevated ABI was 8.4% and that of PAD among these patients 62.2%. PAD was significantly more prevalent among subjects with severe symptoms (rest pain, ulcers or gangrene) than in those with intermittent claudication (83.8% and 45.3%, respectively, p < 0.001). The risk of PAD diagnosis was ten-fold (OR 10.31, 95% CI 2.07–51.30) among those with chronic renal failure, five-fold among patients with a history of smoking (OR 5.63, 95% CI 1.22–26.00) and over three-fold (OR 3.44, 95% CI 1.46–8.12) among those with coronary heart disease. The specificities of elevated ABI threshold levels (1.3, 1.4 and 1.5) in identifying PAD were 86%, 94% and 96%, respectively, the sensitivities being 44%, 38% and 36%, respectively.*
Conclusions. *The prevalence of elevated ABI in patients referred to vascular consultation is 8.4% and that of PAD among these 62.2%. PAD is significantly more probable among those with chronic renal failure, a history of smoking and coronary heart disease. Furthermore, the specificity of elevated ABI (≥1.3) in recognizing PAD is good, whereas the sensitivity is only satisfactory.*

Keywords: Ankle brachial pressure index; Mediasclerosis; Peripheral arterial disease.

Introduction

The prevalence of peripheral arterial disease (PAD) increases with age and affects approximately 20% of the population over 75 years of age.[1] The disorder is associated with high cardiovascular morbidity and mortality but remains an under-diagnosed problem in the primary care setting.[2,3] Ankle brachial pressure index (ABI) measurement with the use of Doppler techniques is an established non-invasive means of diagnosing PAD. The presence of mediasclerosis, however, may invalidate the ABI as a diagnostic tool, as the arterial wall becomes stiffer and resists compression, giving falsely elevated pressure values. In such cases, as the vessels of the toes are generally not affected by mediasclerosis, the measurement of great toe artery pressure for the calculation of the toe brachial index (TBI) is commonly advocated.[4–6] Unfortunately, this method is often available only in specialized vascular units.

The problem of elevated ABI has attracted little attention in the literature on PAD, and no uniform ABI criterion for elevated ABI exists. While some authors have recommended that high ABI be suspected when ABI exceeds 1.15, others have used cut-off values between 1.3 and 1.5.[7–10] The problem of a cut-off value is further underlined by the fact that, especially in younger subjects, ankle pressures normally exceed the systolic pressure of the aorta and brachial vessels due to good arterial wall compliance and strong arterial wave reflection, thus giving a resting ABI over 1.0. Consequently, the proportion of individuals with elevated ankle pressure varies

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between studies and its true prevalence remains obscure. Moreover, the clinical significance of elevated ABI is not as clear as that of low ABI. However, an association between high ABI and total and cardiovascular mortality similar to that of low ABI was found in two recently published studies.[11,12]

The present aims were (1) to establish the prevalence of elevated ankle brachial index among patients admitted to the university hospital vascular outpatient clinic for evaluation purposes; (2) to describe the prevalence and risk factors of PAD among those with elevated ABI; and (3) to assess the specificities and sensitivities of different levels of elevated ABI in identifying PAD.

Material and Methods

Study population

This is a retrospective analysis of consecutive patients referred to the vascular outpatient clinic at Tampere University Hospital (TAUH), Finland, between April 2002 and January 2006. Patients with suspected lower extremity arterial insufficiency were included in the study. The reasons for referral were categorized as (1) intermittent claudication, (2) rest pain, ulcer or gangrene, (3) suspected combined arterial and venous disease and (4) non-specified indication (coldness, numbness). TAUH serves a region with roughly 470,000 inhabitants, and all vascular surgical consultations, diagnostics and procedures are carried out exclusively at TAUH. Patients are referred to the outpatient clinic not only from the municipal health centres but also from regional cardiac, renal and other units located within the TAUH district. Every patient visit to the hospital is recorded in the central register with the diagnosis and reason for attendance. The purpose of the present study was to measure the ankle brachial index (ABI) and toe brachial index (TBI) of all new admissions ($N = 2{,}237$) during the study period. The pressure measurements were unsuccessful in 51 cases (2.3%). Cases with successful measurements and with no prior lower extremity vascular procedures ($N = 1{,}762$, 78.8%) were subjected to further analysis.

Risk factors for PAD and other co-morbid diseases

Data from the patients' files were collected systematically by one examiner (VS). Case records provided information on age, sex, cardiovascular risk factors (diabetes mellitus, hyperlipidaemia, hypertension, smoking within 5 years), cardiovascular diseases other than PAD (coronary heart disease [CHD], cerebrovascular disease), respiratory disease, chronic renal failure and systemic corticosteroid treatment in addition to stored images. The diagnosis for each disease was considered positive if it had been previously established at TAUH or mentioned in the referral, or if the patient was on appropriate medication. No distinction was made between chronic renal failure and ESRD.

Measurement of ABI/TBI and definitions

ABI and TBI were measured using the Nicolet VasoGuard (Nicolet Vascular Inc, Madison, WI), a device that allows simultaneous systolic blood pressure measurements from upper and lower extremities by means of photoplethysmography. Measurements were carried out in optimal conditions (supine position, room temperature, after resting for ten minutes) by trained vascular nurses. Photoplehysmographic probes were attached to the tips of the big toes, and cuffs were placed on the arms and legs above the ankle or at the base of the big toes. The higher of the two simultaneously measured brachial systolic blood pressure values was used in the analysis. As a rule, values obtained from single ABI or TBI measurements of good quality were used. ABI ≤ 0.9 was considered low, ABI > 0.9 or < 1.3 normal and ABI ≥ 1.3 falsely elevated. Patients with an ABI ≤ 0.9 and/or TBI < 0.60 in either leg were regarded as presenting with PAD. Patients with an ABI ≥ 1.3 in both legs or in one leg, in which case the other side had to be normal, were categorized as belonging to the elevated ABI group. The calculations of the sensitivity and specificity of different ABI threshold levels (1.3, 1.4, 1.5) in identifying PAD were based on the results of ABI and TBI measurements.

Review of the angiograms

For 69 patients with an elevated ankle brachial index ($N = 148$), a digital subtraction angiography (DSA) had been performed after the initial consultation. In one patient the TBI was >0.60, while the rest had a TBI < 0.60, i.e. PAD. The angiography images were reviewed for the presence of PAD, defined as a more than 50% narrowing of the arterial lumen in any arterial segment of the lower extremities.

Statistical analysis

SPSS 15.0 for windows was used for statistical analysis (SPSS, Chicago, IL, USA). For discrete variables,

analyses were made with the aid of cross-tabulations combined with χ^2-tests, and comparisons of means between the two groups were carried out with the t-test for independent samples. Logistic regression analysis was used to calculate the likelihood of PAD among those with elevated ABI. *P*-value < 0.05 was considered statistically significant.

Results

The prevalence of elevated ABI

There were 1,041 (59.1%) men and 721 (40.9%) women available for the analysis. The mean age in the cohort was 69.5 ± 11.7 years, the women being almost five years older than the men ($p < 0.001$). The main reason for referral was intermittent claudication ($N = 988$, 56.1%), whereas 553 (31.4%) patients had more severe symptoms (rest pain, ulcers, gangrene). For the remaining 221 (12.6%) patients, the reason for referral was combined arterial and venous disease; otherwise the reason was non-specific. Men were more likely to present with claudication ($p < 0.001$) and women with rest pain ($p = 0.003$).

Low ABI was detected in 1,139 (64.6%) patients; 475 (27.0%) had normal and 148 (8.4%) elevated ABI. The distribution was not affected by sex. The prevalence of low ABI, i.e. PAD, increased steadily with the age of the patients, while the prevalence of high ABI was not dependent on age (Fig. 1). The prevalence of cardiovascular risk factors and other co-morbid conditions as well as systemic corticosteroid treatment between the ABI categories is presented in Table 1.

The prevalence of PAD among patients with elevated ABI

Of the 148 patients presenting with an elevated ABI, 92 (62.2 %) were consequently considered to have PAD. Evaluation of the DSA images confirmed the diagnosis in all 68 available cases. The mean age of patients with PAD was 69.6 ± 12.4 years and of those without PAD 68.9 ± 11.6 years ($p = 0.621$). A non-significant increase in the prevalence of PAD was observed in the older age groups (60% among those below the age of 55 years and 80% among those over 85 years of age, $p = 0.741$). PAD was significantly more prevalent among subjects with severe symptoms than among those referred due to intermittent claudication (83.8% and 45.3%, respectively, $p < 0.001$). According to the logistic regression model, there was a more than ten-fold risk of being diagnosed with PAD among patients with chronic renal failure, five-fold risk among those with a history of smoking and more than three-fold risk among those with CHD (Table 2). The presence of hyperlipidaemia seemed to have a protective effect against PAD (OR 0.3, $p = 0.022$). However, 22 (84.6%) of the 26 patients with hyperlipidaemia were receiving statin treatment.

As 56 patients with an elevated ABI did not have PAD according to the TBI measurements, we further

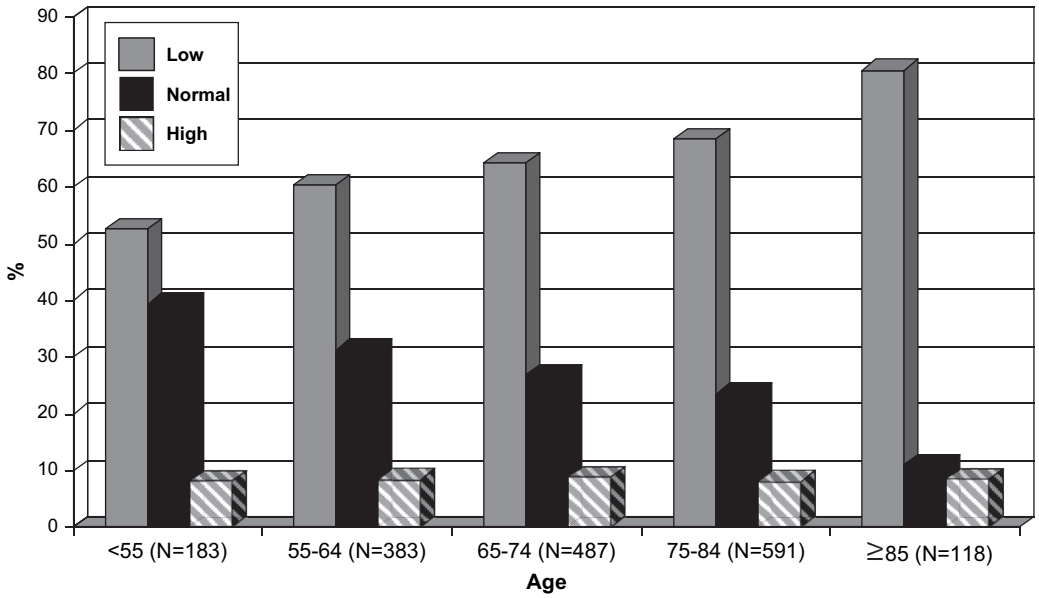

Fig. 1. The distribution of ABI categories according to age.

Table 1. The prevalence of cardiovascular risk factors and comorbid conditions depending on ABI level ($N = 1762$)

Measure	ABI ≤ 0.9	0.9 < ABI < 1.3	ABI ≥ 1.3	*P*-value
	$N = 1139$ (%)	$N = 475$ (%)	$N = 148$ (%)	
Diabetes mellitus	380 (33)	147 (31)	73 (49)	<0.001
Hyperlipidaemia	318 (28)	129 (27)	26 (18)	0.028
Hypertension	604 (53)	210 (44)	64 (43)	0.001
Smoking	374 (33)	76 (16)	15 (10)	<0.001
CHD	397 (35)	134 (28)	57 (39)	0.014
Cerebrovascular disease	122 (11)	43 (9)	12 (8)	0.429
Respiratory disease	140 (12)	36 (8)	18 (12)	0.020
Renal failure	67 (6)	29 (6)	21 (14)	0.001
Systemic corticosteroid treatment	39 (3)	19 (4)	20 (14)	<0.001

assessed the validity of different elevated ABI levels (1.3, 1.4 and 1.5) in identifying PAD. The prevalence of PAD was 78.2% (79/101) among subjects with an ABI > 1.4 and 83.5% (76/91) among those with an ABI > 1.5. Of the 475 patients with normal ABI, 118 (24.8%) had a TBI < 0.6. By pooling the normal and elevated ABI groups, i.e. all subjects with an ABI > 0.9 ($N = 623$), and then defining the number of patients in the combined groups who had a TBI < 0.6 ($N = 210$), we were able to determine the respective specificities and sensitivities. The specificities were good, with a tendency to increase with elevation of the threshold level (86%, 94% and 96%, respectively), whereas the sensitivities were only satisfactory (44%, 38% and 36%, respectively).

Discussion

According to our findings, the prevalence of elevated ABI among patients referred to the vascular outpatient clinic was 8.4%, which was not affected by age or sex. The prevalence of PAD among those with elevated ABI was 62.2%. A significant association between PAD and clinical signs of critical limb ischemia (rest pain, ulcer, gangrene) as compared to claudication was observed at presentation. Furthermore, we found a significant likelihood of being diagnosed with PAD among subjects with chronic renal failure, a history of smoking and CHD. Our results also suggest that the specificity of elevated ABI (≥1.3) in recognizing PAD is good, whereas the sensitivity remains not more than satisfactory.

Table 2. The odds of being diagnosed with PAD among those with elevated ABI ($N = 148$)[*]

Measure	OR	95%CI
Diabetes	1.66	0.76–3.63
Hyperlipidaemia	0.30	0.11–0.84
Hypertension	0.72	0.33–1.57
Smoking	5.63	1.22–26.00
CHD	3.44	1.46–8.12
Cerebrovascular disease	1.32	0.34–5.17
Respiratory disease	1.47	0.46–4.70
Renal failure	10.31	2.07–51.30
Systemic corticosteroid treatment	1.87	0.55–6.30
Sex (male)	1.77	0.75–4.22
Age (per 10 years)	1.26	0.89–1.80

Dependent factor: PAD according to the angiographic findings and TBI.
[*] Logistic regression model.

The prevalence of PAD has been evaluated in several epidemiological studies, falling within the range of 3%–10% and increasing to 20% in persons over 75 years.[1] PAD, regardless of the symptoms, has been associated with increased cardiovascular morbidity and mortality.[1,13,14] Therefore, the control of cardiovascular risk factors—including hypertension, hyperlipidaemia and platelet antiaggregation medication—is important in this population. Unfortunately, only roughly one third of PAD patients exhibit typical symptoms, and the majority are asymptomatic.[2,15,16] It is therefore vital that the general practitioner (GP) is able to diagnose asymptomatic disease, which can only be estimated by means of non-invasive measurements, i.e. ABI measurement. A resting ABI of ≤0.9 is caused by haemodynamically significant arterial stenosis and is most often used in epidemiological studies as a threshold value for the presence of PAD.[16]

Ankle pressures and, consequently, ABI can be falsely elevated due to the use of a too narrow cuff or due to mediasclerosis, which complicates clinical decision-making and PAD diagnosis. In the case of the cuff size, the problem can be avoided by using cuffs that are at least 120% of the diameter of the measuring site.[4,17] If appropriately sized cuffs are used but ABI still remains high, mediasclerosis should be suspected, in which case the measurement of TBI is recommended to diagnose possible PAD.[4-6] In the current study, we used the American College of Cardiology and the American Heart Association (ACC/AHA) recommendations for elevated (noncompressible vessel) ABI, i.e. ≥ 1.3.[18] For TBI, values < 0.6 have been recommended and used as a threshold for PAD.[8,19] The measurement of toe pressure, however, is more time-consuming and technically difficult with the additional equipment required, involving pitfalls of its own—for example, the small vessels of the toes are prone to vasospasm.[20]

The prevalence of elevated ABI varies significantly depending on the study design and threshold values used. Furthermore, these patients are often excluded from studies on PAD and the clinical importance of

elevated ABI thus remains unclear. In 1968 Carter found the incidence of lower extremity vessel incompressibility to be only 1% in a series of 600 limbs studied.[21] In more recent publications, the prevalence has ranged from less than 1% to up to 13.6%, and even higher among diabetic patients.[1,7,10,22] Our results, with a 12.2% prevalence of elevated ABI among diabetic patients versus 6.5% among those without the disease, support this general impression. Two of the aforementioned studies were population-based with a cut-off value of >1.5, which may explain the low prevalence. The material in our study comprised selected patients referred to a vascular surgical unit due to lower limb symptoms and does not represent the whole population. This may also explain the difference in prevalence compared to the results obtained by groups under Diehm and Meijer. Our findings are in line with previous results suggesting that chronic renal failure and systemic corticosteroid treatment are associated with elevated ABI.[8,9] On the other hand, contrary to what has been stated elsewhere,[5,9,23] the prevalence of high ABI was not affected by age.

Since TBI measurement is often available only in specialized vascular units, it would be desirable to have clinical evidence and findings to guide clinicians as to when to suspect PAD among patients with elevated ABI. Our results suggest that elevated ABI itself is markedly associated with PAD and that the specificity increases with the elevation of the ABI values. Furthermore, PAD should be suspected among patients with high ABI combined with chronic renal failure, a history of smoking, CHD and severe lower extremity symptoms. Unfortunately, however, our results show that normal ABI does not exclude the possibility of PAD. This is contradictory to what has been proposed by Brooks and associates regarding the necessity of TBI measurements among subjects with elevated ABI.[24] The large number of patients with normal ABI but pathological TBI in the current material is probably explained by a moderate incompressibility of arteries and, thus, normal ABI in some individuals, even though they actually have poor flow at the ankle level. This reflects the clinical design of the study and is supported by the angiographic data available confirming the diagnosis of PAD in 44 out of 47 patients. This would render the other possible explanation, i.e. technical errors in measuring ABI and TBI, less likely and thus enhances confidence in our sensitivity and specificity calculations. Nevertheless, if vascular surgical consultation is, for any reason, not required or planned, the aforementioned findings should be taken into consideration when planning risk factor management for the particular patient. This is further emphasized by the fact that elevated ABI is associated with significant cardiovascular and total mortality, similarly to low ABI.[11,12] In fact, we believe that our results may even partly explain why such an association exists. Interestingly, however, hyperlipidaemia seems to have a protective effect against PAD. The widespread use of statins accompanied by a reduced intima-media thickness at the carotid and femoral level may explain this effect.[25] The relatively low prevalence of hyperlipidaemia in the present study, probably owing to the study design, reduces the value of this finding.

The device used to measure ABI and TBI in the current study is in clinical use worldwide and has also been employed for research purposes.[8] However, a PubMed search produced no mention of studies on the test-retest reproducibility or validity of this particular equipment. In general terms, pressure measurements have been shown to be reasonably reproducible in previous studies, especially when performed by trained personnel.[26,27] In our institution, the method and device have been used for the past ten years and measurements are undertaken exclusively by trained vascular nurses.

There are several limitations to our study, the main drawback being the retrospective design involving possible data issues associated with the use of hospital discharge histories and patient case records. Consequently, miscoding and lack of clinical information may cause uncertainty in the results. However, the multiple admissions of the subjects to our hospital due to co-morbidities prior to the initiation of the current study made data collection easier and, we believe, more accurate. Furthermore, possible data errors and miscoding will be similar for all groups. The second limitation is the clinical nature of the study, with a relatively high prevalence of elevated ABI. This certainly affects any generalization of the present results, especially in terms of the general population.

Conclusions

According to our findings made in a clinical setting, the prevalence of elevated ABI is 8.4%. The prevalence of PAD among patients with elevated ABI is 62.2%, and it is significantly more probable among those with chronic renal failure, a history of smoking and CHD. Furthermore, our study confirms the high prevalence of PAD among patients with severe lower leg symptoms and high ABI. The specificity of elevated ABI ($\geq$1.3) in identifying patients with PAD seems to be good, whereas its sensitivity in excluding the

disease is only satisfactory. These findings may provide guidance in clinical decision-making associated with this problem, especially in patients with chronic renal failure. Further studies are warranted to determine a generally acceptable cut-off value and thereby the true prevalence and significance of elevated ABI.

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Peripheral arterial disease and its clinical significance in nonagenarians

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ABSTRACT. ***Background and aims:*** *The purpose of this study was to characterize the prevalence and clinical features of peripheral arterial disease (PAD) among 90-year-old individuals and to assess its relationship to lower extremity functional status and survival over one year.* ***Methods:*** *A prospective, population-based study of all 90-year-old residents of Jyväskylä, Finland. Fifty-eight out of the 79 registered residents were examined for ankle-brachial index (ABI). Lower extremity functional status was assessed as self-reported difficulty in performing specific physical activities of daily living (PADL). In a subgroup of 36 individuals, lower extremity functioning was further assessed by measuring walking endurance and walking velocity. Death dates were collected for one year after the examination from the hospital register.* ***Results:*** *Thirteen persons (22%) had an ABI<0.9. PAD was asymptomatic in 11 of them and the diagnosis of PAD new to 12 of them. Thirty (52%) subjects had a normal ABI (0.9-1.4) and in 15 (26%) cases the ABI was pathologically high (>1.4). A significant accumulation of cardiovascular risk factors was observed among those with an ABI<0.9 compared with those with normal or high ABI (2.0±0.8* vs *1.3±0.8* vs *1.5±0.5,* p=*0.03). Those with low or high ABI reported more difficulties in the PADL tasks than those with normal ABI, but the results did not reach statistical significance. No difference in maximal walking velocity was observed according to ABI in the subgroup with data available. After one year, nine people had died, of whom only two (7%) with normal ABI and seven with low or high ABI (25%)* (p=*0.05).* ***Conclusions:*** *PAD was found to be mainly asymptomatic among 90-year-old people. An abnormal ABI was also associated with increased mortality risk over a one-year follow-up. Although our study was small-scale, it does provide novel information about the prevalence of PAD and clinical significance of ABI in very old people. (Aging Clin Exp Res 2008; 20: 211-215)*

INTRODUCTION

Together with the overall aging of the population, there is also a clear increase in the number of very old people (90+). In Finland, the number of individuals over 90 years of age almost doubled between 1994 and 2004, and currently accounts for 0.5% of the total population (1). It is estimated that this figure will be 0.8% by 2020 (almost 44,000 individuals) (2). The life expectancy of 90-year olds in Finland in 2004 was 4.03 years (3). Peripheral arterial disease (PAD) affects predominantly older people and the prevalence increases with age. However, the prevalence and clinical features of PAD in nonagenarians are not known. According to the available literature, PAD is an under-diagnosed problem in the primary care setting (4, 5).

PAD is associated with high cardiovascular morbidity and mortality due to atherothrombotic events, which frequently occur among persons with PAD regardless of whether they have symptoms or not (6-8). Recently, the results of two epidemiological studies suggest that mortality risk associated with an ABI>1.4 is comparable to that with an ABI≤0.9 (9, 10). Although the relationship between PAD and lower extremity function has not been well studied, there is some evidence of a correlation between ankle-brachial pressure index (ABI) and lower extremity functional impairment. In the study by McDermott et al., PAD and ABI were found to be independent predictors of walking endurance and walking velocity over short distances (11). A lowered ABI has also been shown to be associated with lower physical activity (12). These functional deficits can affect the ability to live independently in the community (13, 14).

Key words: Functional status, lower extremities, nonagenarians, peripheral arterial disease.

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The purpose of this study was to characterize the prevalence, clinical features and significance of PAD among 90-year-old individuals in a non-clinical setting. Attention was paid to the management of PAD risk factors and the use of antithrombotic agents. The relationship between PAD and lower extremity functional impairment was also assessed, as well as the association of ABI with survival over one year.

MATERIALS AND METHODS

Participants

This study forms part of the Evergreen project (15). The target group consisted of all the 90-year-old residents (n=79) of the city of Jyväskylä, Finland, who, at the beginning of the project in 1989, at the age of 75, were community-dwelling. The current study was conducted between November 1 and December 31, 2004. Twenty-one eligible candidates declined to participate. Thus, 58 (73%) people formed the current study group. The participants were followed until the end of December 2005. Any dates of death were obtained from patients' case records at Jyväskylä Central Hospital.

Peripheral arterial disease (PAD)

The presence of PAD was evaluated by measuring systolic blood pressure at both brachial arteries, the dorsal pedal artery and the posterior tibial artery, in both left and right leg on an 8-MHz continuous-wave Doppler probe (Handydop, Kranzbühler, Germany) and a manual sphygmomanometer. For each artery, a single blood pressure reading was taken with the subject in a supine position after 10 minutes' rest. The ratio of the highest systolic blood pressure value obtained for each leg to the highest value for the arm was calculated. PAD was defined as an ankle-brachial pressure index (ABI) of less than 0.9 in either leg. ABI values above 0.9 and below 1.4 were considered normal. An ABI greater than 1.4 was defined as high (9). During the physical examination, participants were asked if they experienced intermittent claudication or pain at rest, and possible signs of critical limb ischemia (ulcers or gangrene) were recorded. The clinical presentation of PAD was described according to the Fontaine classification (16).

Cardiovascular risk factors

Cardiovascular risk factors included: smoking, hypertension, diabetes and hypercholesterolemia. Participants were divided into three groups, depending on their smoking habits: current smokers, ex-smokers and non-smokers. Hypertension was defined as a systolic blood pressure of 160 mmHg or higher, a diastolic blood pressure of 95 mmHg or higher, treatment for hypertension, or a history of hypertension. Diabetes was defined as a diagnosis by a physician, use of medication, or non-fasting blood glucose ≥11.0 mmol/L. Hypercholesterolemia was defined as a total cholesterol level higher than 6.45 mmol/L, diagnosis by a physician, or use of cholesterol medication. The presence of CHD and CVD was ascertained during the interview, and was defined as a diagnosis by a physician.

Lower extremity functional status

Lower extremity functional status was characterized on the basis of direct observation and self-report. Those who were bedridden and reported severe difficulty in moving indoors, moving outdoors or negotiating stairs were categorized as having severe mobility limitation. Those who reported no or little difficulty were assigned to the reference group.

In a subgroup of 36 participants, lower extremity functional status was further studied at the research center. To assess walking endurance, subjects walked for 6 min (12). If necessary, they were allowed to rest. The distance achieved at the end of 6 min was recorded. Walking velocity was assessed by walking a 10-meter distance at maximal pace. The walk was performed once and time-recorded. Walking velocity was calculated by dividing 10/recorded time.

Statistical analysis

The SPSS 13.0 program for Windows was used for statistical analyses (SPSS, Chicago, IL, USA). For discrete variables, analyses were carried out with the help of cross-tabulations together with $\chi 2$ tests, and comparisons of means between two groups were carried out with the *t*-test, and between three groups with One-Way ANOVA.

RESULTS

Peripheral arterial disease

ABI was measured in 47 (81%) women and 11 (19%) men. The prevalence of PAD was 22% (13/58). Except for one person with a previous femoral amputation due to gangrene in the foot (Fontaine IV), all cases detected were new. One person had intermittent claudication (Fontaine II). Thus, the prevalence of asymptomatic disease was 85%. Twenty-six percent of the participants (15/58) had an ABI>1.4. High ABI was somewhat more common among women (13/47) than men (1/11) but the difference did not quite reach statistical significance (p=0.12). One person with high ABI was on corticosteroid therapy, three had diabetes, and none had end-stage renal disease (ESRD).

Cardiovascular risk factors

Table 1 lists the distribution of cardiovascular risk factors and other cardiovascular diseases according to ABI. The differences in the prevalence of individual risk factors were not statistically significant. However, the accumulation of risk factors among those with an ABI<0.9 was

Table 1 - *Cardiovascular risk factors and presence of other cardiovascular diseases depending on ABI level (n=58).*

Measure	ABI<0.9 n=13 (%)	0.9≤ABI<1.4 n=30 (%)	ABI≥1.4 n=15 (%)	*p*-value*
Smoking, ever	3 (23)	3 (10)	2 (14)	0.52
Hypertension	10 (77)	16 (53)	8 (53)	0.31
Diabetes	4 (31)	6 (20)	3 (20)	0.71
Hypercholesterolemia	9 (69)	12 (40)	9 (60)	0.61
Coronary heart disease	8 (62)	14 (47)	8 (53)	0.66
Cerebrovascular disease	3 (23)	4 (13)	4 (29)	0.51
Number of risk factors (mean±SD)	2.0±0.8	1.3±0.8	1.4±0.5	0.03

*χ^2 test was used for categorical and One-Way ANOVA for continuous variables.

significantly higher compared with the other two groups (p=0.03).

Risk factor management

Almost half (6/13; 46%) of the candidates with an ABI<0.9 were not taking any antithrombotic agent. Three of these six individuals also had other cardiovascular diseases. Altogether, nine individuals had a total cholesterol level over 6.45 mmol/L. Four of them were on lipid-lowering therapy. Hypertension was present in ten candidates, of whom five were being treated with antihypertensive agents. All diabetics were receiving medication.

Lower extremity functional status

Table 2 shows the proportions of people reporting severe difficulties in performing specific PADL activities at different ABI levels. In three cases, the results for self-reported activity were not available. Of the remaining 55 individuals, five were bedridden - two with normal ABI, two with ABI>1.4, and one with ABI<0.9. In general, people with low or high ABI reported more difficulties than those with normal ABI, but the results did not reach statistical significance.

Of the 36 individuals examined at the research center, only 23 (64%) completed the six-minute walking test and, therefore, no further analysis was performed with regard to walking endurance. All except one candidate took part in the ten-meter walking test. Maximal walking velocity for those with normal ABI was 1.17±0.40 m/s, for those with low ABI 1.03±0.27 m/s, and for those with high ABI 1.04±0.15 m/s (p=0.51).

Survival

A total of nine participants died during the follow-up: 2 (7%) with normal ABI, 3 (23%) with ABI<0.9 and 4 (27%) with ABI>1.4 (p=0.115). When individuals with an abnormal ABI (either <0.9 or >1.4) were combined into one group, the difference in total mortality became significant compared with those with normal ABI (25 *vs* 7%, p=0.05). Six of the deaths were cardiovascular, one among those with normal ABI, and five among those with abnormal ABI (p=0.07).

Of the 21 eligible candidates who declined to participate in the study, 14 (5 male, 9 female) were interviewed. Eight of them were living at home, and the rest in various long-term care facilities. They had an average of one risk factor for PAD and self-rated health was, in general, satisfactory.

DISCUSSION

According to our study, among 90-year-old people, approximately half had normal ABI, whereas 22% had PAD and 26% high ABI. In most cases, PAD was asymptomatic and had not been detected earlier. Persons with ABI<0.9 had significantly more risk factors than those with normal or abnormally high ABI. Risk factor man-

Table 2 - *Proportion of people reporting severe difficulties in performing various PADL activities depending on ABI level (n=55).*

PADL task	ABI<0.9 n=13 (%)	0.9≤ABI<1.4 n=29 (%)	ABI≥1.4 n=13 (%)	*p*-value*
Moving indoors	6 (46)	5 (17)	6 (46)	0.07
Moving outdoors	7 (54)	9 (30)	7 (58)	0.23
Negotiating stairs	7 (54)	8 (28)	6 (46)	0.21
Any PADL task	7 (54)	11 (38)	8 (62)	0.32

*χ^2- test.

agement was not optimal with regard to hypertension, hypercholesterolemia and antiplatelet therapy. In addition, a significantly poorer survival among those with abnormal ABI was observed over a one-year follow-up.

The prevalence and clinical features of PAD in nonagenarians has not been studied before. In previous studies, the overall prevalence of PAD ranged between 20 to 50%, and was even higher in the highest age groups (>85 years) (4, 6, 17, 18). According to these studies, the prevalence steadily increases from age 50 onwards and peaks at age 85 and over. The decrease in the prevalence of PAD in nonagenarians, found in the current study, is probably explained by the accelerated mortality rate of older people in their late 80s, since only the fittest and healthiest survive into their 90s. Even so, this selective mortality does not seem to make PAD, with typical risk factor profile and prognosis, a rare phenomenon in nonagenarians.

High ABI is the result of vessel wall stiffness due to mediasclerosis, mainly caused by diabetes, end-stage renal disease and systemic corticosteroid treatment (19-21). However, no uniform ABI criterion for high ABI exists. Some authors have recommended that high ABI should be suspected when ABI exceeds 1.15; others have used a cut-off value between 1.3 and 1.5 (12, 17). Consequently, the proportion of individuals with elevated ankle pressure varies in different studies and its true prevalence is not known. Although the clinical importance of high ABI is not as clear as low ABI, an association between high ABI and total and cardiovascular mortality similar to that of low ABI was found in two recently published studies (9, 10).

In the EU, the proportion of individuals over 80 is expected to rise by 45% between 2004 and 2020 (22). In Finland, during the same period, a 60% rise in the number of individuals over 90 is anticipated (2). At the same time, the life expectancy of very old people is growing, and even for nonagenarians, it is over four years (3). The aging of the population is expected to lead to a significant increase in the demand for vascular services. In Finland by 2020, increases of 35% in procedures for claudication and 44% for critical limb ischemia have been estimated (23). As PAD seems to be asymptomatic in the majority of people over 90, the number of vascular procedures needed among this age group would be limited.

The association between PAD and cardiovascular morbidity and mortality is well established and intensive atherosclerotic risk factor management is uniformly recommended (4, 6-8). However, the question of secondary prevention among nonagenarians is controversial and has been little studied. At the same time, polypharmacy among very old people is common and is often accompanied by complications (24-26). According to the criteria suggested by Beer et al. and updated by Fick in 2003, there are currently 48 potentially inappropriate drugs, some of which should never be used in elderly people (27, 28). This also concerns antithrombotic agents, especially when used together with anticoagulant therapy. Therefore, although a thorough evaluation of the risks and benefits of cardiovascular risk factor modification needs to be carried out among very old people, nonagenarians should not be denied secondary prevention just because of their high age.

Although most patients will never require revascularization or amputation, PAD still affects lower extremity functioning, even in asymptomatic patients. An ABI<0.9 has been shown to be correlated with reduced walking velocity and walking endurance, and the association between ABI reduction and degree of impairment seems to be linear (11). The fact that PAD is associated with increased muscle fiber deficiencies of the lower extremities supports these clinical findings (29).

Lowered ABI has also been shown to be associated with lower physical activity when measured with an accelerometer (12). Although commonly used to determine functional status in the elderly (30), PADL measurements have not previously been used to assess the relationship between ABI level and lower extremity functioning. According to our results, defining ABI may perhaps be used in nonagenarians to identify individuals at higher risk for mobility loss.

The small sample size of our study, and the fact that toe pressure was not measured to diagnose PAD in high ABI participants, are the main limitations of our study. Had we been able to measure toe pressure, we would probably have detected more cases of PAD. The current results do not allow us to draw conclusions on the relationship between PAD and lower extremity functioning. Nevertheless, our study provides novel information about the presence and clinical features of PAD and the status of peripheral circulation in individuals aged 90 years. This information may be generalized to other similar populations, considering the participation rate of 73%, which is good in target population of such a high age. Our results suggest that nonagenarians can be recruited into population-based studies, and that larger clinical or non-clinical trials among very old people are needed to better understand health changes among very old people.

It is important, however, that for the first time an attempt has been made to describe the prevalence and clinical features of PAD in nonagenarians.

CONCLUSIONS

According to our study, the prevalence of PAD is 22% and the prevalence of high ABI is 26% in 90-year-old individuals. In most cases, PAD is asymptomatic and risk factor management is not optimal. Abnormal ABI values also seem to be associated with poorer one-year survival in nonagenarians. More studies are needed to determine the possible relationship between PAD and mobility loss in very old people.

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Absent pedal pulse and impaired balance in older people: a cross-sectional and longitudinal study

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ABSTRACT. ***Background and aims:*** *The purpose of this study was to determine the relationship between abnormal pedal pulse status and postural balance in older people.* ***Methods:*** *Prospective, population-based cohort study of older residents in the city of Jyväskylä, Finland. A total of 419 individuals aged 75 or 80 at baseline, with known lower extremity pulse status and balance tests performed on a force platform, were eligible for analysis.* ***Results:*** *Cross-sectionally, persons with both dorsal pedal artery pulses absent were found to sway more (*p=*0.047 anteroposterior velocity, normal standing eyes-open position). The risk of being unable to do the full tandem stance was twofold (OR=2.20, 95% CI 1.29-3.78) for persons without palpable dorsal pedal arteries compared with those with normal pulse status. Balance deterioration was observed at five years (*p<*0.001for time) but without group-by-time interaction. At ten years, however, the interaction term became significant for the normal standing eyes-closed position (*p=*0.025 for anteroposterior velocity and* p=*0.026 for mediolateral velocity), indicating greater balance deterioration among those with both dorsal pedal artery pulses absent.* ***Conclusions:*** *According to our study, the absence of both dorsal pedal artery pulses is associated with impaired balance in older people. The association was observed both cross-sectionally and longitudinally. In addition, as diminished pedal pulses are frequently associated with impaired lower extremity circulation, our results have also produced information on the possible pathophysiological mechanisms of balance deterioration in older people, which warrant further study.*

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INTRODUCTION

The ability to control postural balance is an important determinant of safe mobility. Older people commonly report impairment in balance. Deterioration of balance with age is also suggested by cross-sectional studies, older people typically obtaining poorer results (1-3). To date, only a few studies have evaluated prospective changes in postural balance (4, 5). The etiology and mechanisms of impaired balance with age remain imperfectly studied and, again, only very few studies have addressed this issue.

Impaired circulation and tissue oxygenation jeopardizes normal organ functioning. Loss of lower extremity muscle mass and strength has been associated with chronic illnesses such as chronic obstructive pulmonary disease and congestive heart failure (6, 7). Recently, a similar connection has been established between lower extremity arterial obstructions and impaired leg strength (8). The relationship has been shown in patients with peripheral arterial disease (PAD), regardless of their symptoms (9, 10). However, the relationship between reduced arterial flow to the lower extremities and impaired balance has been little studied. The results of existing studies indicate that persons with PAD are prone to disturbances in balance (10, 11).

Even today, with the large variety of diagnostic equipment available, a thoroughly performed physical examination remains the basic diagnostic tool for physicians. Consequently, as a method accessible to all clinicians, pulse palpation is an important component of the clinical examination to detect possible arterial disease. Distal pressure and the palpability of an artery have been shown to be correlated (12). However, factors such as arterial anatomy, vessel size, edema, diabetic changes, and observer error may affect the reliability of the examination (13, 14). It is widely accepted, therefore, that the diagnosis

Key words: Balance deterioration, older people, pedal pulse, physical examination.

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of any peripheral arterial condition should not be based solely on the results of distal pulse palpation.

The aim of the present study was to examine changes in postural balance in a non-clinical, population-based sample of elderly community-dwelling individuals with normal and abnormal pedal pulse status detected during a physical examination. The analysis was done both cross-sectionally and longitudinally. The predictive value of abnormal pulse status for a person's overall performance and prognosis was also evaluated.

MATERIALS AND METHODS

Participants

This study forms part of the Evergreen Project, a population-based prospective study on the health of older residents in the city of Jyväskylä, Finland (15). The initial study group consisted of community-dwelling people (n=665) who were either 75 or 80 years old at baseline. Follow-up studies were conducted at five and ten years. For the current study, we chose participants who at baseline had pedal pulse status recorded and had done at least one balance test. 419 individuals (137 men, 282 women) were eligible for further analysis. 220 subjects attended the 5-year follow-up. Of the remaining 217 individuals, 135 had died, 64 were only interviewed at home, had refused to participate further in the study, or were unable to perform any of the balance tests. At ten years, 248 of the initial 419 participants had died, and 78 had dropped out. Thus, 93 individuals formed the 10-year follow-up group. The Ethical Committee of the University of Jyväskylä approved the initial study design.

Clinical examination

Baseline physical examination of all participants was done by the same experienced physician. Palpation findings for femoral and dorsal pedal arteries (ADP) were recorded in the study protocol as either present or absent. In this study, subjects were divided into three groups according to findings: both ADP pulses present, one ADP pulse absent, and both ADP pulses absent. Chronic conditions, including cardiovascular risk factors such as smoking, hypertension, diabetes, hypercholesterolemia and obesity (BMI>25), were also ascertained during the clinical examination. Participants were divided into three groups depending on their smoking habits; current smokers, ex-smokers, and never smokers. Hypertension and diabetes were defined as self-reported or medication use for the condition. The presence of other cardiovascular and respiratory diseases were ascertained in the same manner. Body weight and height were measured in the laboratory and the body mass index (BMI) was calculated. Blood tests to determine serum total and high density cholesterol (HDL) were taken. Almost all patients had a total cholesterol level >5.0 mmol/L; hence, we used the total cholesterol/HDL ratio to determine unfavorable cholesterol status. Results >5.0 were considered as unfavorable.

Balance tests

Balance was measured on a piezoelectric force platform (Kistler 9861 A) with an area of 600 mm x 1200 mm. The piezoelectric transducers located in each corner of the platform recorded the vertical, anteroposterior and mediolateral horizontal forces, independently of each other. Signals were amplified (Kistler amplifier) and stored in a multi-channel analogue recorder (Racal 7). The method is described in detail elsewhere (16). Three different tests were done while subjects were standing on the platform: 1) normal standing for 40 seconds with eyes open (EO), hands placed on hips, feet comfortably apart, and gaze fixed on a mark at eye level; 2) normal standing, as before, for 40 seconds, but with eyes closed (EC); 3) tandem standing (feet positioned heel-to-toe along the midline of the platform) for 20 seconds. The tests were performed in the same order for each subject, starting with the easiest test and then advancing to the more difficult ones. For each test, three balance outcome variables were calculated: anterior-posterior sway velocity, mediolateral sway velocity, and velocity moment. The last variable refers to the first moment of velocity calculated as the mean area covered by the movement of the center of force during each second of the test, taking into account both distance from the geometrical midpoint of the test and speed of movement during the same period. Because a significant number of participants were unable to perform the most challenging test, these results were left out of the current analysis. The likelihood of a person not being able to perform the test was calculated instead, and results are presented with a 95% confidence interval. The relationship between pulse status and a participant being able to attend the 5- and 10-year follow-up, was also assessed.

Statistical methods

The SPSS 11.5 program for Windows was used for statistical analyses (SPSS, Chicago, IL, USA). For discrete variables, analyses were done with the help of cross-tabulations together with χ^2-tests, and comparisons of means between two groups were carried out with the *t*-test for independent samples. A general linear model was used in variance analysis to determine possible interactions between pulse status, age and gender. The likelihood of a person not being able to perform the most demanding balance test at baseline was calculated by linear regression analysis. The effects of time and pulse status on balance were assessed by one-way ANOVA for repeated measures.

RESULTS

Baseline status and cross-sectional analysis

For 137 men and 282 women, pedal pulse status had been recorded and at least one balance test was performed at baseline. 223 of the participants were age 75 and 196 age 80. 266 subjects had normal pulse sta-

Table 1 - *Baseline characteristics of participants.*

Measure	%
Male gender	33
Smoking, ever	29
Hypertension	23
Diabetes	8
Tot. Chol/HDL-C >5	47
BMI >25	65
Coronary heart disease	35
Cerebrovascular disease	9
Chronic obstructive pulmonary disease	9
Congestive heart failure	16
	Mean±SD
Number of cardiovascular risk factors*	2.1±1.1
Weight, kg	68.1±11.3
Height, cm	160.3±8.7

*Cardiovascular risk factors: male gender, smoking, hypertension, diabetes, unfavorable lipid status, obesity.

tus, i.e., both ADP pulses were palpable. 42 participants were lacking one and 111 were lacking both ADP pulses. The prevalence of coronary heart disease was significantly higher in the group with both ADP pulses absent (45.0%) compared with the group with normal ADP pulses (32.3%) or one absent pulse (28.6%) (p=0.039) (Table 1). The prevalence of other chronic illnesses did not differ according to pulse status. The distribution of PAD risk factors (male gender, smoking, hypertension, diabetes, unfavorable lipid status, obesity) among the groups was also equal. The prevalence of diabetes was 8.4%.

Cross-sectional analysis of the balance tests between the three groups according to ADP pulse status is shown in Table 2. Individuals with both ADP pulses absent had the worst recordings in the tests, whereas statistical significance was reached only in the normal standing eyes-open position (p=0.047) in anteroposterior sway. The association was present but non-significant in the normal standing eyes-closed position (p=0.088 for anteroposterior sway). The interaction term for pulse status and age/gender did not reach statistical significance. 88 participants were unable to perform the most demanding test with full tandem standing. The number of non-performers was significantly higher among those with both ADP pulses missing, compared with those with one absent pulse or normal pulse status (29% *vs* 17% *vs* 16% respectively, p=0.012). The odds ratio for persons with both ADP pulses missing not being able to hold the tandem stance for 20 seconds was double (OR=2.20, 95% CI 1.29-3.78) compared with those with normal pulse status.

Prospective analysis

Prospective analysis was done separately for those attending only the 5-year follow-up (n=109) and for those attending both 5- and 10-year follow-ups (n=93). As the results of the balance measurements were similar for individuals with normal and one absent ADP pulse in the cross-sectional analysis, we combined these two groups for the longitudinal analysis (control group) and compared the results with those lacking both ADP pulses.

Balance deterioration over time (p<0.001 for time) was observed for the 5-year follow-up group without group-by-time interaction. At ten years, the group-by-time interaction term became significant for the normal standing eyes-closed position, in which persons with absent ADP pulses had poorer results in both anteroposterior and mediolateral sway (p=0.025 and 0.026 respectively). No systematic interaction between gender and pulse status was observed. Figure 1 shows overall changes in balance over time in the normal standing eyes-closed position. Gender distribution was equal across the ADP status groups, men accounting for approximately one-third in each group at five and ten years. The groups were also similar by age. Absence of both ADP pulses did not seem to have any value in predicting a person's ability to attend the follow-up, either at five or ten years (OR=1.54,

Table 2 - *Cross-sectional analysis of balance in normal standing eyes-open (EO) and eyes-closed (EC) (mean±SD)* tests.*

Parameter	Normal	Missing one ADP	Missing both ADP	p-value** for trend
Normal standing EO	(n=263)	(n=39)	(n=109)	
Anteroposterior velocity, mm/s	21.16±6.70	21.27±6.21	23.19±8.30	0.047
Mediolateral velocity, mm/s	12.15±3.53	12.85±4.09	12.94±5.24	0.191
Velocity moment, mm^2/s	44.46±23.68	46.23±21.27	47.73±30.76	0.522
Normal standing EC	(n=260)	(n=41)	(n=109)	
Anteroposterior velocity, mm/s	29.08±10.28	27.30±7.30	31.21±13.53	0.088
Mediolateral velocity, mm/s	15.35±5.26	15.05±4.95	16.56±9.73	0.251
Velocity moment, mm^2/s	71.06±44.48	4.66±33.92	84.09±92.76	0.100

*402 participants performed both tests, 9 eyes-open test only, and 8 eyes-closed test only. **One-way ANOVA.

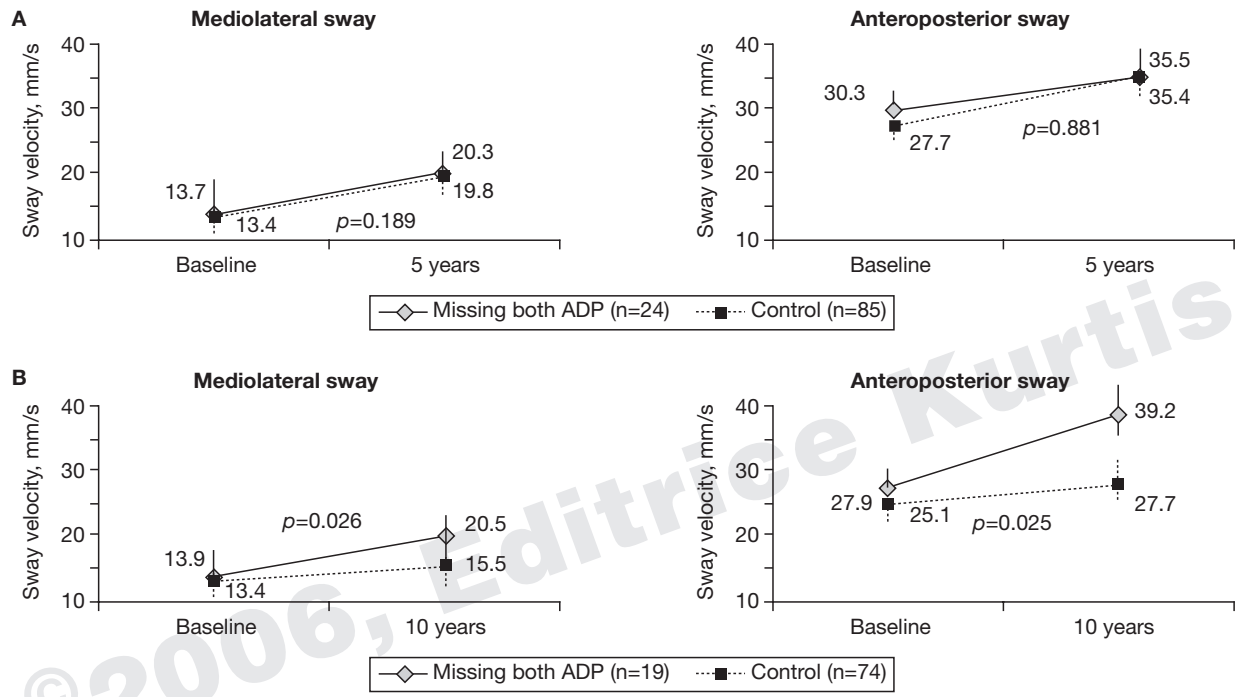

Fig. 1 - *Changes in balance over time according to pulse status (normal standing EC position, mean). A: at five years, B: at ten years (p=group by time interaction).*

95% CI 0.98-2.40 and 1.40, 95% CI 0.85-2.40 respectively, for persons lacking both ADP pulses). Nor did it predict the risk of death during the 10-year follow-up.

DISCUSSION

In the present study, it was found that abnormal pedal pulse status was associated with impaired balance in older people. The association was present both cross-sectionally and longitudinally. In addition to poorer results in the actual balance tests, individuals with both ADP pulses absent were also found to be at a double risk of not being able to hold a full tandem stance for 20 seconds. Deterioration in balance at five years was similar, regardless of baseline pulse status. The impact of time on balance performance had been reported earlier, with similar results (4, 5). At ten years, the interaction term between time and pulse status became significant. More importantly, the interaction became significant in the more challenging, normal standing eyes-closed position, in which balance is increasingly dependent on information from the proprioceptive and mechano-receptive organs. As people grow older, there is a general deterioration in the number of musculoskeletal and sensory systems affecting postural control and balance. Balance disorders are particularly important, because they decrease the social autonomy of older people and often provoke falls. As the cause of balance impairment is always multifactorial, it is important to study all the possible pathophysiological mechanisms leading to it.

Physical examination remains the basic diagnostic tool for clinicians. Pulse palpation is inexpensive and sometimes the only available method to evaluate peripheral circulation. There are a number of reasons for absent ADP pulses, and they may be divided into three categories: 1) the dorsal pedal artery does not exist, i.e., it is congenitally absent, 2) the dorsal pedal artery or proximal vessels are stenosed/occluded; 3) the arterial pulse cannot be detected, due to observer error or other problems such as local edema. The prevalence of congenitally absent ADP varies in different studies, and clearly depends on the character of the study. In the study by Robertson et al., in which 547 healthy young subjects were examined by digital palpation and a doppler probe, ADP was found to be absent in 15 subjects (3%) bilaterally or unilaterally (17). Yamada et al. found ADP absent in 6.7% cases in their study on cadavers (18). The presence of peripheral arterial disease definitely should be suspected in persons with diminished ADP pulses (12). This especially concerns older people, as the prevalence of PAD increases with age. Other chronic conditions which may lead to lower extremity artery stenosis or occlusion are diabetes and, more rarely, inflammatory vascular diseases. The preva-

lence of absent ADP due to a previous vascular trauma is likely to be very low; however, no estimates have been published.

The validity of pulse palpation has been widely studied. The relationship between absent pedal pulses and PAD has been the main focus of interest. Some authors have concluded that abnormal pedal pulse, as a clinical finding, helps clinicians diagnose the presence of PAD (19), while others have concluded that pulse palpation enables physicians to exclude the diagnosis of PAD to a high degree of certainty (20). Lundin et al. studied the reliability of distal pulse palpation in 25 patients (13). They came to the conclusion that pulse palpation should not be used as the sole method in the diagnosis of PAD, due to the high proportion of misdiagnoses and poor agreement between palpation findings and measured ankle-brachial index (ABI). Some investigators, while questioning the reliability of pedal pulse palpation, have shown training to improve results (12).

It has been proposed that muscle weakness partly explains the poorer functioning of the postural control system in the elderly (1, 16). Conversely, loss of lower extremity muscle mass and strength has been associated with chronic illnesses such as chronic obstructive pulmonary disease, congestive heart failure, and PAD (6-8). The pathophysiological mechanism behind this phenomenon is thought to be chronically impaired tissue oxygenation, resulting in increased muscle fiber deficiencies (21, 22). In our sample, the prevalence of chronic obstructive pulmonary disease and congestive heart failure was similar in each group and, therefore, does not explain the results. Nor was there any difference in the prevalence of cerebrovascular disease between the groups, so that central nervous system dysfunction hardly explains the poorer balance performance among those with absent pedal pulses. As ABI was not measured, we cannot make conclusions about the association between PAD and impaired balance. Nevertheless, we believe that the possible link between an absent pedal pulse and poorer balance is worsened lower extremity circulation, together with loss of muscle strength. Whether this is due to PAD or other vascular diseases and conditions remains to be established. To date, only a few studies have addressed the issue. The results of these studies indicate that individuals with PAD, symptomatic or asymptomatic, are prone to balance disturbances and have a greater likelihood of falling compared with their counterparts without PAD (10, 11).

As diabetes has previously been associated with increased disability and poorer physical functioning (23), we assume that persons with diabetic polyneuropathy also sway more due to worsening of exteroceptive information. In the current study, the number of diabetics was low and the presence of polyneuropathy among them was unknown. However, with equal prevalence in each group, diabetes is an unlikely explanation for our results. In addition to diabetes, peripheral polyneuropathy has been associated with worsening circulation. In a clinical study by McDermott et al., patients with PAD were found to have higher degree of neuropathy than those without PAD (9). In their study of the pathophysiological mechanisms of peripheral polyneuropathy, Teunissen et al. found that chronic ischemia played some role in the development of the phenomenon (24, 25).

The method used to measure balance in this study has been increasingly popular recently. Good test-retest reproducibility of the standing balance tests had previously been reported (26, 27). The method also demonstrates good validity, for example, in studies testing the effects of balance training on postural control (28). The use of a computerized force platform made it possible to measure balance quantitatively and to detect smaller differences or changes than would have been possible in tests of the categorized performance type, which often have ceiling and floor effects disturbing the interpretation of results.

The reproducibility, accuracy and validity of pulse palpation are the potential limitations in our study. Unfortunately, no other measures of circulation were carried out at the baseline of this interdisciplinary study. False negative and false positive findings are likely to be found to some extent, although the physician doing the pulse palpation was highly experienced and worked in non-hurried and otherwise good conditions. All in all, it is more important to consider an absent pedal pulse as a sign of a possible chronic disease rather than to ignore it. Another potential issue in our data is the loss to follow-up resulting from studying an elderly sample over a long period. At baseline, all participants were either 75 or 80 years old and community-dwelling individuals. This made it a rather homogeneous study group, with few confounding factors at baseline. Less than a quarter of the group was available for the 10-year follow-up. In general, the prevalence of chronic illnesses affecting circulation, such as coronary heart disease, cerebrovascular disease, hypertension and diabetes, was greater among those who did not attend the follow-ups. Had the current sample been followed up at shorter intervals, there would have been a greater possibility of detecting the pathophysiological effects of these diseases on balance, thus potentially reinforcing findings. Consequently, we believe that selective mortality caused our findings to be underestimated rather than overestimated in their effects.

Identifying all the possible pathophysiological mechanisms of postural control loss is the key to the prevention of balance impairment. Despite the small number of subjects, our study does give new information about the possible factors underlying poor balance. However, further study is warranted, to determine the pathophysiological mechanisms explaining the association between absent pedal pulses and poor postural balance.

CONCLUSIONS

According to the results of our study, the absence of both dorsal pedal artery pulses on palpation is associated with deterioration in balance in older people. The association was observed both cross-sectionally and longitudinally. This association has clinical importance, as it may help clinicians to identify those at increased risk of balance disturbances. Furthermore, as diminished pedal pulses are frequently associated with impaired circulation of the lower extremities, our results also produce information on the possible pathophysiological mechanisms of deterioration in balance in older people. More studies are needed to assess the association between absent pedal pulses, worsened circulation of the lower extremities, and postural balance.

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Peripheral arterial disease, diabetes and postural balance among elderly Finns: population-based study

Running heading: Peripheral arterial disease and balance

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ABSTRACT

Background and aims: Little is known about the role of peripheral arterial disease (PAD) in the development of balance impairment. The aim of this study was to assess postural balance among people having PAD or PAD combined with diabetes.

Methods: As a part of the comprehensive health examination of the Health 2000 survey (two-stage stratified cluster sampling), 1,323 people aged 65 years or older took part in balance assessments using a force platform system. The presence of PAD was confirmed using data from the National Hospital Discharge Registry. Individuals with hospitalization due to PAD were regarded as having severe disease, while those with a solely self-reported diagnosis were considered possible cases. Diabetes was ascertained on the basis of self-reported physicians' diagnoses subsequently confirmed in a clinical examination.

Results: 45 (3.4%) individuals had previously been hospitalized due to PAD, and 32 (2.4%) reported that they had been diagnosed with the disease. 413 (31%) participants had diabetes. Compared to people without PAD, those with confirmed diagnosis exhibited significantly increased movement of the centre of pressure while standing, indicating deteriorated balance. Those with possible PAD formed an intermediate group. The presence of diabetes exacerbated the deterioration in balance, but the interaction term between PAD and diabetes did not reach statistical significance. The risk of failing the tandem stance tests was over three-fold (OR=3.20, 95%CI 1.09–9.37) among those with confirmed PAD and almost one and a half-fold (OR=1.44, 95%CI 1.07–1.93) among those with diabetes in comparison to those without these diseases.

Conclusions: Individuals over 65 years of age with severe PAD showed increased balance impairment, a known risk factor for falls and disability in aged people. Diabetes affected balance somewhat less than PAD, but there was no formal evidence of synergetic effect of the two diseases. Additional studies are indicated to reveal the possible effect of proper treatment of PAD

and diabetes combined with suitable training interventions on slowing down the progression of balance impairment.

Introduction

Impaired lower extremity functioning is an important predictor of disability and nursing home placement among aged people (1). One of the main determinants of normal functioning is the ability to maintain postural balance. Due to the complexity of the balance control system, deterioration in balance can rarely be explained by a single factor. Few studies have investigated the role of chronic illnesses in balance impairment. There is, however, some evidence that peripheral arterial disease (PAD) and diabetes have a negative impact on balance control.

PAD has been shown to reduce leg strength and lower extremity functioning in general (2). According to the literature, the relationship is present regardless of the symptoms of PAD (3, 4). Muscle weakness, on the other hand, has been proposed as a candidate for balance impairment (5). This and ischemic neuropathy present among those with severe PAD are both possible explanations for the association between PAD and impaired balance found in the existing literature (3, 4, 6, 7).

Diabetes is one of the main risk factors for PAD, and it has become increasingly common in individuals with PAD. In two recently published studies approximately 30% of primary care patients with PAD had diagnosed diabetes (8, 9). As with PAD, diabetes is also associated with increased disability and poorer physical functioning, especially among older people (10). Furthermore, diabetes has been shown to cause balance impairment, predominantly among those with known neuropathy (11, 12).

As impaired lower extremity functioning can ultimately restrict one's ability to live independently in the community, it is an important public health objective to recognize all the potential factors that could lead to mobility loss. The purpose of this study was to assess the association of postural balance with PAD alone and with PAD combined with diabetes in a nationally representative sample of persons aged 65 years and over.

Material and methods

Participants

This study forms part of the Health 2000 survey conducted by the National Public Health Institute (KTL), Finland, between August 2000 and June 2001. Detailed information on the survey has been published elsewhere (13). The two-stage stratified cluster sampling design was planned by Statistics Finland. The initial sample consisted of 8,028 individuals. The target group for the current study was defined as those aged 65 years or older (N=2194). 1,490 (68 %) individuals participated in a comprehensive health examination at one of the research centres. Of these initial 1,490 individuals, balance tests (at least the easiest) on a force platform were performed for 1,323 (60%) participants; 167 (11%) did not perform any of the balance tests, mostly due to technical problems with the force platform system. Patients who declined to participate in the study, or who were interviewed or examined at home, were excluded from the current study.

Peripheral arterial disease

Whether the participants had been diagnosed with PAD or not was elicited by the question "Has a doctor diagnosed arterial stenosis in the lower extremities?" Information about hospitalization due to PAD was obtained from the Research and Development Centre for Welfare and Health (STAKES) using the appropriate ICD 8–10 codes (4402, I70.2). Participants with a solely self-reported diagnosis were classified as having "possible PAD" and those with hospitalization, i.e. with more severe disease, as having "confirmed PAD". During the interview participants were also asked whether they had claudication or not. No other information with reference to clinical features of PAD was available.

Diabetes and other PAD risk factors

Information on diabetes was based on a self-reported diagnosis by a physician ascertained during the health examination, the use of diabetes medication or fasting glucose ≥ 6.1 mmol/l. No distinction was made between type I and type II diabetes. Depending on the presence of PAD (possible + confirmed) and diabetes, four groups were then formed: individuals with PAD and diabetes (PAD+DM), individuals with PAD (PAD), individuals with diabetes (DM) and individuals without PAD and diabetes (NORMAL). Self-reported information about the presence of diabetic neuropathy was available only in 178 (43 %) out of 413 cases and was therefore not analyzed separately. Hypertension and hypercholesterolaemia were defined as a diagnosis by a physician—or, for hypertension, systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg measured from the person's right arm in a sitting position after a five-minute rest using a Mercuro 300 mercury manometer and, for hypercholesterolaemia, a markedly increased fasting total cholesterol level (≥6.5 mmol/l). Participants were also asked about smoking and were classified as non-smokers, ex-smokers or current smokers.

Chronic illnesses

Self-reports of the presence of chronic diseases with possible effect on postural balance (congestive heart failure, COPD, cerebrovascular disease including TIA, stroke, haemorrhage, Parkinsonism) as well as coronary heart disease were confirmed by a physician during the health examination

Balance tests

Balance was measured using the Good Balance system for measuring postural sway (Metitur Ltd., Jyväskylä, Finland). The system consists of an equilateral triangular force platform,

connected to a computer through a 3-channel amplifier with an A/D-converter and a computer programme (14). Four different tests were performed while the subjects were standing on the platform: 1) normal standing for 30 seconds with eyes open (EO), feet comfortably apart, arms in a relaxed position in front of the body with one hand gripping the wrist of the opposite arm, and gaze fixed on a mark at eye level (distance 2 meters); 2) normal standing as before for 30 seconds, but with eyes closed (EC); 3) semi-tandem standing (the first metatarsal joint of one foot besides the calcaneus of the other foot) eyes open for 20 seconds with the arms hanging freely at the sides so that they could be used for balance correction if necessary; and, finally, 4) tandem standing (feet positioned heel to toe along the midline of the platform) with eyes open for 20 seconds and arms positioned as in the semi-tandem test. The tandem test was performed only if the participant was able to hold the semi-tandem position for 10 seconds.

The tests were performed in the same order for every subject, starting with the easiest test and advancing to the more difficult ones. If the subject was not able to perform the test (e.g. the eyes were opened before the end of the second test or the position of the feet changed during the semi-tandem or tandem test), he/she was allowed another trial of the same test. For each test, two balance outcome variables were analysed: anterior-posterior (AP) and mediolateral (ML) sway velocity (mm/s). Sway velocity characterizes the displacement of centre of pressure (COP) during each second of the test. Outcome variables were adjusted for height. The methods used in the Health 2000 survey to test balance have been described in detail previously (15).

Statistical analysis

The analyses were conducted using SPSS 14.0 software with Complex Samples for Windows (SPSS, Chicago,IL, USA), which takes the sampling design into account. The observations were weighted to reduce bias due to non-response and to correct for over-sampling

of those aged 80 and older (17). Cross-tabulation was used for discrete variables together with the chi-square-test. A general linear model was used to determine the relationship between postural balance and PAD (PAD± DM). The association between PAD, DM and PAD+DM with the likelihood of a person not being able to perform the most demanding balance test was calculated by logistic regression analysis. The model-based analyses were adjusted for age, sex and other confounding factors. P-values<0.05 were considered statistically significant.

Results

PAD

Data on 567 (43%) men and 756 (57%) women were available for the analysis. The mean age was 74.5±7.0 years with no significant sex difference. Information on hospitalization due to PAD was available in 45 cases (3.4%). An additional 32 (2.4%) participants reported that they had been diagnosed with the disease. Of those with a confirmed diagnosis, 41 (91%) were currently suffering from claudication, while for those with a self-reported diagnosis, the corresponding figure was 16 (50%).

PAD risk factors and other chronic diseases

Table 1 summarizes the distribution of PAD risk factors and other chronic diseases among those who performed at least one (the easiest) balance test. A total of 413 (31%) individuals had diabetes, and the diagnosis was new to 264 of them. Of the 149 participants with known diabetes, 39 (26%) did not use any medication, 27 (18%) were on insulin therapy, 67 (45%) used tablets and 16 (11%) received combined therapy. In addition to diabetes, male sex and smoking were significantly more common in individuals with PAD. Otherwise, the distribution of PAD risk factors was equal in each group. However, a significant accumulation of PAD risk factors was observed among patients with a confirmed diagnosis. Furthermore, individuals with possible or confirmed PAD had a tendency to suffer more frequently from congestive heart failure.

Balance

Table 2 presents the results of the balance tests between the three groups according to the certainty of PAD diagnosis. Participants with a confirmed, i.e. severe, PAD swayed significantly more than those with a possible diagnosis or those without PAD in all tests.

The balance behaviour between the four groups according to the presence of PAD and diabetes is shown in Figure 1. The number of individuals in the PAD+DM and PAD groups proved relatively low (11 and 8, respectively) in the third test with semi-tandem standing, and therefore only the first two tests were analyzed. When formally tested, the interaction term for PAD and PAD did not reach statistical significance in any of the analyzed tests.

Of the 1,323 participants for whom an attempt at the first two tests was possible, 572 (43%) were unable to perform the most challenging balance test (tandem-standing). A more than three-fold risk for not being able to do the most challenging test was observed among the subjects with severe PAD (OR=3.20, 95%CI 1.09–9.37) and an almost one and a half-fold risk (OR=1.44, 95%CI 1.07–1.93) among those with diabetes, when compared to those without these diseases (Table 3).

Discussion

According to our findings, individuals over 65 years of age with severe PAD showed increased balance impairment, assessed as increased sway on the force platform**.** Although the presence of diabetes seemed to worsen the deterioration in balance, our results did not show any synergistic effect of PAD and diabetes. Finally, individuals with severe PAD or DM were at greater risk for not being able to perform the most demanding balance test.

Maintaining postural balance is a complex physiological process involving the interaction of many body subsystems: biomechanical elements, several sensory modalities, muscles and joints, and the central nervous system (17). Consequently, the mechanisms of balance impairment are also multifactoral. A decline in the ability to control postural balance with increasing age has been suggested in cross-sectional studies (18). However, age alone does not explain the changes in the subsystems involved in balance control. The presence of chronic illnesses, such as PAD and diabetes, can affect regulation within and between these systems, and can ultimately lead to balance deterioration. Proper treatment of these diseases, combined with suitable training interventions, may delay the progression of balance impairment.

The prevalence of PAD increases with age and affects approximately 20% of the population over 75 years of age (19). The majority of patients with PAD are asymptomatic or have leg symptoms other than classic intermittent claudication (20). Recently PAD, irrespective of the presence of symptoms, has been shown to reduce lower-extremity muscle mass and strength (3, 4). Chronically impaired tissue oxygenation resulting in increased muscle fibre deficiencies is considered to be the pathophysiological mechanism explaining the phenomenon (21). Whatever the aetiology of muscle weakness may be, it has been proposed that muscle weakness of the lower extremities partially explains the poorer functioning of the postural control

system in the elderly (5). Reduced arterial flow to the lower extremities can also cause peripheral neuropathy, especially among those with severe PAD, which in turn worsens balance control (7).

To date, the possible association of PAD and impaired balance has attracted limited attention. Some of the studies suggesting that the relationship exists have used only one test (normal standing EO) to define balance deterioration, and there is no longitudinal data available. According to the existing studies, individuals with PAD, symptomatic or asymptomatic, are prone to balance disturbances and are at a greater risk for falls than their counterparts without PAD (3, 4, 6, 7).

Diabetes mellitus is highly associated with PAD and its progression. In a primary care setting, approximately 30% of PAD patients suffer from diabetes, and the figure increases to up to 40% among those requiring hospitalization due to PAD (8, 9, 22). The overall prevalence of diabetes in the current study was high, which reflects the current status of the diabetes epidemic in Finland. Furthermore, our findings are in line with previous results, suggesting that the prevalence of diabetes among Finns aged 70 years or older is over 20% and the proportion of impaired glucose tolerance over 30% (23). Diabetes is not only a risk factor for PAD-associated mortality and lower extremity amputation, but due to peripheral neuropathy with loss of sensation in the feet, the condition also affects the postural control system (11, 12). However, there is evidence suggesting that not all changes in gait characteristics among diabetics are explained by peripheral neuropathy but that they are, instead, neurological in origin (24).

Again, studies on the balance behaviour in patients with PAD accompanied with diabetes are few. Dolan and co-authors found that PAD patients with diabetes had poorer lower extremity function, including balance, than those with PAD alone (25). According to the authors, the difference in function was probably due to diabetes-related neuropathy and cardiovascular disease. Although the differences between diabetics and non-diabetics were most marked in

indicators of balance, balance was tested with only one test (feet together side by side), which may affect the interpretation of the results.

Today, COP-based indicators are most often used to characterize postural steadiness. The introduction of a computerized force platform as used in the current study has made it possible to measure balance quantitatively and to detect smaller differences or changes than would have been possible through tests of the categorized performance type, which often have ceiling and floor effects confounding the interpretation of the results (15). Good test-retest reproducibility has previously been reported for the standing balance tests (15, 26). Both AP and ML sway velocity, rather than absolute sway measurements, have been shown to be sensitive indicators of imbalance (15, 27). Moreover, it has been suggested that especially increased ML sway may be an indicator of the propensity to fall (27). However, according to a recent review, the small number of studies in this field makes it difficult to draw definitive conclusions between force platform data and subsequent falls (28).

There are three potential limitations to our study. First of all, no objective method of diagnosing PAD was used. In Finland, the Research and Development Centre for Welfare and Health (STAKES) and its predecessors have collected information about hospitalization due to any reason (National Hospital Discharge Register) since 1969 by means of appropriate ICD-codes, and this procedure is a statutory obligation. The validity of the register has been tested previously with reference to coronary heart disease and stroke (29, 30). According to these studies, the validity is good. Therefore, the number of individuals with a confirmed PAD diagnosis can be considered reliable as well. Miscoded diagnoses in the register may, however, mean that some patients have been missed in our study. On the other hand, missing information about hospitalisation for PAD does not exclude a possible visit to a vascular out-patient clinic for diagnostic purposes. The less severe disease, with no need for previous vascular interventions,

probably explains the better balance results found among those with a possible diagnosis only. Furthermore, the overall prevalence of symptomatic disease (5.8%) in the current sample is in concordance with studies on the epidemiology of PAD (8, 20). Although the agreement between self-reported diagnosis of PAD and medical records is considered moderate (31), we believe that the use of the self-reported information in this context is not totally unjustified. In fact, it is likely to underestimate rather than overestimate the relationship between PAD and impaired balance.

Secondly, as information about diabetic neuropathy was available only for one third of the diabetic patients, we can only discuss the effect of diabetes on balance control on the general level. Unfortunately, the sample size was too small for further subgroup comparisons. Thirdly, 60% of the target group was available for the current analysis, while the participation of the highest age group (80+) in the balance tests was only 41%. Consequently, one must be cautious when evaluating the results. The nationally representative study sample, however, allows us to make generalisations, to an extent, about the relationship between PAD, diabetes and postural balance on the national level.

The current study shows that two very prevalent diseases among aged people are associated with balance deterioration. This gives the clinician a tool for recognizing those possibly at greater risk for mobility loss and nursing home placement. Our data also imply that additional studies are indicated to reveal the possible effect of proper treatment of PAD and diabetes combined with suitable training interventions on slowing down the progression of balance impairment.

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Table 1. The distribution of PAD risk factors and other chronic diseases among those who performed at least the easiest balance test (N=1323)

Measure	Confirmed PAD (N=45) N(%)*	Possible PAD (N=32) N(%)*	PAD not present (N=1246) N(%)*	p-value
Age (Mean±SD)	75.1±6.9	73.3±5.9	73.9±6.7	0.411
Male sex	26(64)	19(51)	522(40)	0.013
Smoking				<0.001
current	9(22)	4(13)	111(10)	
previous	18(46)	14(44)	321(27)	
non-smoker	17(32)	14(44)	811(64)	
Diabetes	31(70)	12(37)	370(29)	<0.001
Hypertension	29(66)	18(54)	773(62)	0.754
Hyperlipidaemia	11(24)	9(29)	447(36)	0.200
Coronary heart disease	14(34)	9(27)	251(20)	0.104
Cerebrovascular disease	7(13)	4(12)	111(9)	0.295
COPD	1(8)	3(3)	47(3)	<0.001
Congestive heart failure	12(26)	9(28)	153(11)	0.001
Number of risk factors (Mean±SD, max 5)	2.8±1.1	2.3±1.1	2.0±1.1	<0.001

* numbers are un - weighted, percentages weighted values

Table 2. Cross-sectional analysis of balance in normal standing eyes-open (EO) and eyes-closed (EC) and semi-tandem positions (mean±SD)*

Parameter	Confirmed PAD	Possible PAD	PAD not present	p-value
Normal standing EO	N=45	N=32	N=1246	
Anteroposterior velocity, mm/s	11.96±6.43	9.85±3.70	8.70±3.70	0.003
Mediolateral velocity, mm/s	7.09±4.00	5.60±2.38	5.02±2.50	0.004
Normal standing EC	N=45	N=32	N=1208	
Anteroposterior velocity, mm/s	23.86±16.00	16.96±6.31	14.84±7.70	0.002
Mediolateral velocity, mm/s	12.24±10.09	8.12±3.94	7.04±4.18	0.007
Semi-tandem	N=31	N=25	N=1031	
Anteroposterior velocity, mm/s	20.61±8.37	18.18±10.78	16.39±7.31	0.032
Mediolateral velocity, mm/s	25.48±10.90	21.27± 8.72	19.67±8.92	0.010

* adjusted for age, sex, smoking, diabetes, COPD, congestive heart failure, and number of risk factors

Table 3. The odds for not being able to perform the tandem-standing test among those with PAD or diabetes as compared to people without these diseases. Logistic regression model.

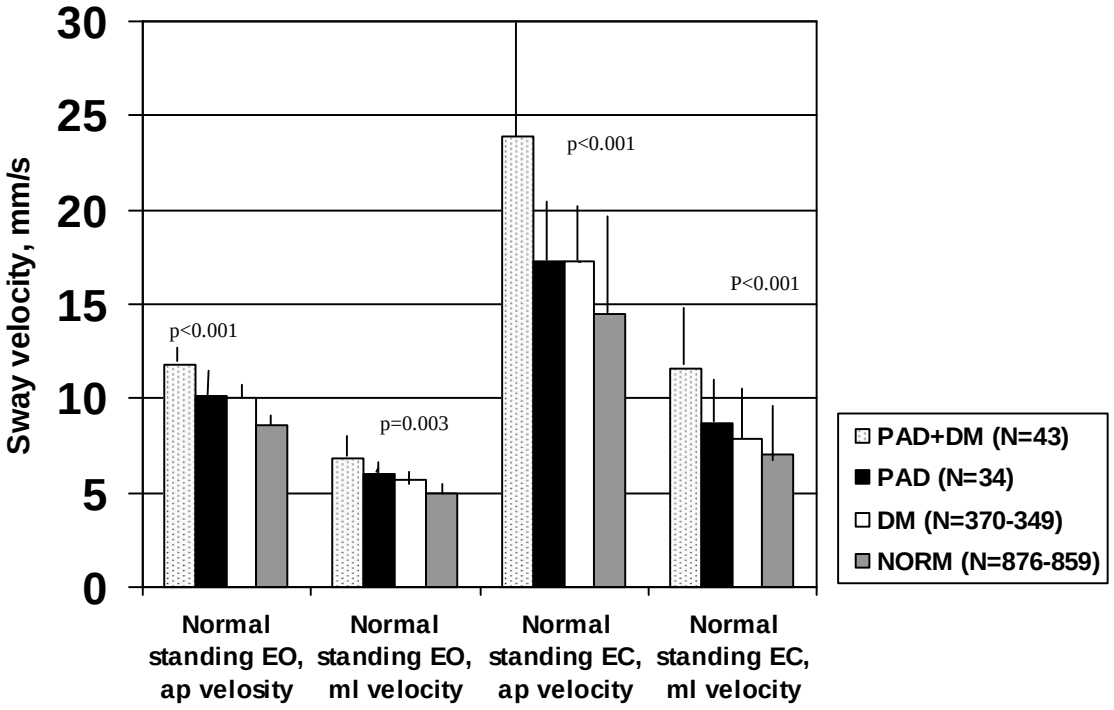
Measure	OR	95%CI
	Unadjusted analyses	
Confirmed PAD	2.64	1.04-6.85
Possible PAD	1.12	0.50-2.53
DM	1.59	1.25-2.03
PAD*+ diabetes	1.67	0.57-4.88
	Partially adjusted analyses **	
Confirmed PAD	2.76	1.05-7.21
Possible PAD	1.06	0.46-2.45
DM	1.59	1.24-2.05
PAD*+ diabetes	1.92	0.65-5.70
	Fully adjusted analyses #	
Confirmed PAD	3.20	1.09-9.37
Possible PAD	1.17	0.47-2.95
DM	1.44	1.07-1.93
PAD*+ diabetes	2.28	0.69-7.53

* confirmed + possible cases
** adjusted for sex, smoking, COPD, and congestive heart failure
# adjusted for age, sex, hypertension, hyperlipidaemia, coronary heart disease, cerebrovascular disease, COPD, and congestive heart failure

Figure legends

Figure 1. Balance behaviour according to the presence of PAD and diabetes

(Mean±SE)*



* adjusted for age, sex, smoking, COPD, congestive heart failure, and number of risk factors