

HEIKKI HIETANEN

Ankle Blood Pressure as a Predictor of Vascular Events

The background of the cover is white and features a decorative pattern of numerous blue, semi-transparent spheres of varying sizes. These spheres are scattered across the page, with some appearing larger and more prominent than others, creating a sense of depth and movement. The spheres have a subtle texture and are rendered with soft shadows, giving them a three-dimensional appearance.



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Ankle Blood Pressure as a Predictor
of Vascular Events



ACADEMIC DISSERTATION

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the Board of the School of Medicine of the University of Tampere,
for public discussion in the small auditorium of building M,
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of Vascular Events

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ABSTRACT

In clinical settings the ankle BP is measured exclusively for the calculation of ankle-brachial pressure index (ABI) for the diagnosis of peripheral arterial disease. Both, high and low ABIs are recognized as clinically important markers of atherosclerotic disease due to their strong associations with cardiovascular disease incidence and mortality. The value of ankle blood pressure itself has not been evaluated. This study is based on the hypothesis that in the beginning of the arterial stiffening and atherosclerosis the ankle blood pressure may be determined by blood pressure and the elastic properties of conduit arteries. The elevated ankle blood pressure might be one of the earliest signs of adverse changes in the cardiovascular system. On the other hand, stenotic changes along the conduit vessels decrease the ankle blood pressures, but cause exaggerated exercise blood pressure and this group has to be considered as a separate entity.

Subjects for this investigation were derived from a group of 4,038 consecutive ambulatory patients, who underwent symptom-limited bicycle exercise test at the Helsinki Deaconess Institute between August 1989 and December 1995. The patients were referred by occupational health physicians to a symptom-limited exercise test to rule out coronary heart disease and evaluate physical fitness. Patients with a documented history of cardiovascular disease were excluded from the analysis. The final study group consisted of 3,858 patients.

Subjects were divided into five groups based on resting ankle and exercise blood pressure at the moderate exercise level. Groups were constructed because they made sense pathophysiologically and because the ankle blood pressure has a U-shaped association with the risk of a coronary event and cannot therefore be analysed as a continuous variable. As there are no established reference values for the ABP or the brachial exercise blood pressure, we chose our cut-points (175 and 215 mmHg) arbitrarily to create groups of reasonable size. In the reference group the resting ankle blood pressure was <175 mmHg and the exercise blood pressure \leq 215 mmHg.

The all cause mortality follow-up data were available for up to 15 years. Data on coronary death or first non-fatal coronary event, including MI, percutaneous coronary angioplasty or coronary artery bypass graft surgery, were available for up to 15 years and the follow-up for incident cerebrovascular events was 16 years and for incident dementia 18 years.

Results were expressed as hazard ratios (HR) and 95% confidence intervals (CI) compared to the reference group. The basic models were adjusted for age and sex. The

larger models were further adjusted for BMI, physical working capacity (metabolic equivalents = METs), self-reported blood glucose and cholesterol, current smoking and early parental history of cardiovascular disease.

This study confirmed that the ankle blood pressure gives us important information about the status of the arterial tree in middle-aged asymptomatic individuals. The main finding was that even those persons among whom the elevated ankle blood pressure was the only abnormal finding had 1.7-fold higher multivariate-adjusted risk of death, especially cardiac or cerebrovascular death (2.2 and 3.3-fold). The elevated ankle blood pressure had an independent predictive value even for dementia (1.6-fold), probably due to its role as a marker of arterial stiffness or atherosclerosis. On the other hand, persons with normal ankle, arm and exercise brachial blood pressure had clearly the best prognosis. The total mortality was 5.7%, mortality due to cardiac causes was only 0.95% and due to cerebrovascular causes 3.5% during the follow-up of 18 years.

In conclusion, an abnormal increase in ankle blood pressure with or without exaggerated exercise BP reaction may act as a forewarning of increased CV risk to clinicians, irrespective of resting BP. Wider use of the ankle BP measurement in clinical work seems warranted.

ABSTRAKTI

Nilkka-olkavarsipainesuhdetta eli ABI-mittausta käytetään alaraajojen valtimoverenkierron arviointiin. Perinteisesti matala ABI-arvo ($\leq 0,90$) tarkoittaa perifeeristä stenoottista valtimotautia. Viime vuosina myös korkea ABI-arvo ($\geq 1,4$) on pidetty poikkeavana mittaustuloksena.

Nilkkapaineen merkitystä – ilman ABI-suhdetta – ei ole selvitetty. Tämän tutkimuksen perushypoteesina on että verisuonten jäykistyessä (stiffness) ja sklerosoituessa (atherosclerosis) nilkkaverenpaine nousee, johtuen sekä verenpaineesta että paikallisista verisuonimuutoksista, ja nilkkaverenpaineen nousu on yksi varhaisimmista poikkeavista kardiovaskulaarista muutoksista. Hypertoninen rasitusverenpaineeste ilman nilkkaverenpaineen nousua erottaa toisaalta ne potilaat, joilla alaraajojen stenoottinen muutos ahtauttaa jo alaraajojen verenkiertoa.

Tutkimusaineisto koostuu 4038 potilaasta, joille tehtiin Helsingin Diakonissalaitoksessa kliininen rasituskoe elokuun 1989 ja syyskuun 1995 välisenä aikana. Valtaosa potilaista olivat työterveyslääkärien lähettämiä. Indikaationa olivat fyysisen kunnan selvittäminen, sydänlihaskemian toteaminen tai rasitusastman selvittely. Kun diagnosoituiden sydänsairaat poissuljettiin, jäi lopulliseksi aineistoksi 3858 potilasta.

Potilaat jaettiin viiteen eri ryhmään perustuen nilkka- ja rasitusverenpaineeseen. Ryhmittäminen oli tarpeen, sillä nilkkaverenpaineen yhteys sydän- ja verisuonitautiriskiinkin ei ole lineaarinen. Koska nilkkaverenpaineesta eikä rasituksen aikaisesta verenpainevastestakaan ei ole olemassa viitearvoja, ryhmät muodostettiin niin, että kukin ryhmä oli tilastanalyysijä ajatellen tarpeeksi iso. Referenssiryhmän muodostivat potilaat, joilla nilkkaverenpaine oli korkeintaan 175 mmHg ja rasituksen aikainen systolinen verenpaine kohtuullisella kuormalla korkeintaan 215 mmHg.

Kokonaiskuolleisuutta seurattiin 15 vuotta, sepelvaltimotautitapahtuman tai -kuoleman ilmaantumista samoin 15 vuotta ja sairaalahoitoon tai kuolemaan johtaneiden aivoverenkiertohäiriöiden ilmaantumista seurattiin 16 vuotta sekä dementoitumista 18 vuotta.

Potilasryhmällä, jolla ainoana poikkeava löydöksenä oli nilkkaverenpaineen nousu yli 175 mmHg, oli referenssiryhmään verrattuna 1,7-kertainen riski kuolla seurannan aikana. Erityisesti sydän- ja aivoverenkiertosairauksista johtuva kuolleisuus oli merkittävä (2,2–3,3-kertainen). Myös dementoituminen oli korostunut (1,6-kertainen). Toisaalta referenssiryhmän sairastuvuus ja kuolleisuus oli muihin ryhmiin nähden merkittävästi pienempää: kokonaiskuolleisuus 5.7 %, sepelvaltimotautisairastuvuus vain 0.95 % ja sairastuvuus aivoverenkierron häiriöihin 3.5 %.

Nilkkaverenpaineen nousu joko ainoana poikkeavana löydöksenä tai yhdessä hyper-tonisen rasitusreaktion kanssa on poikkeava löydös, merkinä suurentuneesta riskistä sairastua sydän- tai aivoverenkiertosairauksiin tai myöhemmällä iällä dementoitua. Nilkkaverenpaineen mittauksen nykyistä laajempi käyttö kliinisessä työssä vaikuttaa aiheelliselta.

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LIST OF ORIGINAL COMMUNICATIONS

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

- I Hietanen H, Pääkkönen R and Salomaa V. Ankle blood pressure as a predictor of total and cardiovascular mortality. *BMC Cardiovascular Disord* 2008; 8: 3
- II Hietanen H, Pääkkönen R and Salomaa V. Ankle and exercise blood pressures as predictors of coronary morbidity and mortality in a prospective follow-up study. *J Hum Hypertens* 2010; 24: 577–584
- III Hietanen H, Pääkkönen R and Salomaa V. Ankle Blood Pressure and Pulse Pressure as Predictors of Cerebrovascular Morbidity and Mortality in a Prospective Follow-Up Study. *Stroke Res Treat* 2011; 2010: 729391
- IV Hietanen H, Pietilä A, Kähönen M and Salomaa V. Ankle blood pressure and dementia: a prospective follow-up study. *Blood Pressure Monitoring* 2013; 18: 16–20

ABBREVIATIONS

ABD	ankle-brachial pressure difference
ABI	ankle-brachial index
AHA	American Heart Association
Aix	augmentation index
ASCVD	atherosclerotic cardiovascular disease
BP	blood pressure
CABG	coronary artery bypass graft surgery
CHD	coronary heart disease
CKD	chronic kidney disease
CRP	C-reactive protein
CV	cardiovascular
CVD	cardiovascular disease
CNS	central nervous system
cIMT	carotid intima media thickness
cPP	central (aortic) pulse pressure
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
eNOS	endothelial NO synthase
EVD	endothelium-dependent vasodilation
FMD	flow-mediated dilatation
FRS	Framingham Risk Score
GFR	glomerular filtration rate
HDL	high-density lipoprotein
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein

HYVET	Hypertension in the Very Elderly Trial
ICD	International Classification of Diseases
IMT	intima-media thickness
LDL	low-density lipoprotein
Lp(a)	lipoprotein(a)
LVH	left ventricular hypertrophy
MCI	mild cognitive impairment
NO	nitric oxide
OD	subclinical target organ damage
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
PWV	pulse wave velocity
RAAS	renin-angiotensin-aldosterone system
RCT	randomized controlled trial
RR	relative risk
SBP	systolic blood pressure
SCORE	Systematic Coronary Risk Evaluation Project
SNA	sympathetic nerve activity
SNS	sympathetic nervous system
WHO	World Health Organization

1 INTRODUCTION

There are several established procedures for assessing subclinical changes in human arteries. Pulse pressure is perhaps the oldest one and has been used as a crude indicator of arterial stiffness. Pulse wave velocity is related to stiffness of the arterial wall, future hypertension and vascular diseases. Coronary artery calcium screening and evaluation of endothelial dysfunction are the latest methods for assessment of arterial subclinical damage.

Patients with exaggerated exercise blood pressure reaction have increased cardiovascular and cerebrovascular morbidity, although its value has been debated for decades. The elevated exercise blood pressure is observed when the cardiac output is not balanced by increased compliance from dilatation of peripheral muscle vasculature, i.e., early vascular stiffness caused by structural changes and/or exaggerated sympathetic response. Growing evidence exists, that the exaggerated exercise blood pressure is an important marker of cardiovascular disease (CVD), associated with incident hypertension and vascular mortality. In addition, it promotes endothelial dysfunction by reducing the availability of nitric oxide.

The ankle blood pressure is usually measured in conjunction with the brachial blood pressure when stenotic peripheral changes are suspected. Decreased ankle-brachial pressure index (ABI) is strongly associated with vascular diseases. Nowadays, an elevated ABI, a measure of mediasclerosis, seems to be also a significant risk factor of CVD.

We hypothesized that in the beginning of the arterial stiffening and atherosclerosis the ankle blood pressure may be determined by systemic blood pressure and the elastic properties of conduit arteries. The elevated ankle blood pressure might be one of the earliest signs of adverse changes in the cardiovascular system. On the other hand, stenotic changes along the conduit vessels decrease the ankle blood pressures, but cause exaggerated exercise blood pressure and this group has to be considered as a separate entity.

Long-term prospective studies on the value of ankle blood pressure in middle-age persons are sparse and the aim of the present study was to assess the independent value of ankle blood pressure, together with the brachial exercise blood pressure, as a predictor of vascular mortality and morbidity.

2 REVIEW OF THE LITERATURE

2.1 Blood pressure regulation

A fundamental law of the circulation is that arterial pressure is the product of cardiac output and total peripheral resistance. The regulation of blood pressure involves a variety of organ systems including the central nervous system (CNS), cardiovascular system, kidney, and adrenal glands. These systems modulate cardiac output, fluid volume, and peripheral vascular resistance as the major determinants of blood pressure. The body has several important systems for controlling blood pressure, which react within seconds (baroreceptors, chemoreceptors, and CNS ischemic response), minutes (the RAAS, stress relaxation, capillary fluid shift, and aldosterone release), and finally hours or days (renal volume control) (Guyton AC 1991). The kidney is the dominant mechanism for the long-term regulation of blood pressure (pressure natriuresis and renin-angiotensin system) (Guyton AC 1991). Renal transplantation studies further support the central role of the kidney in regulating blood pressure (Rettig and Grisk 2005).

Increasing clinical evidence indicates that sympathetic nervous system plays a critical role in the control of arterial pressure. Sympathetic nerves are continuously active so all innervated blood vessels remain under some degree of continuous constriction.

By rapidly regulating the level of activity, the degree of vasoconstriction in the blood vessels of many key organs around the body is altered. This in turn increases or decreases blood flow through organs, affecting the function of the organ, peripheral resistance, and arterial pressure.

Carotid baroreflex activation affects peripheral sympathetic nerve activity that is under the control of the carotid sinus baroreceptors. They are effective in counteracting acute changes in arterial pressure causing a tonic inhibitory action on cardiovascular centers. Whether arterial baroreflexes affect long-term control of sympathetic activity controlling long-term blood pressure and supplying reliable information about the actual level of blood pressure, is controversial (Lohmeier TE et al. 2004, Guyton AC et al. 1969, Lohmeier TE et al. 2005, Thrasher TN 2006). Recent studies indicate that the chronic activation of the carotid baroreflex reduces blood pressure, heart rate, and plasma norepinehrine levels suggesting the presence of an inhibitory influence, likely baroreflex-mediated renal sympathoinhibition, affecting on the renin release (Weir MR and Dzau VJ 1999).

A second short-term blood pressure control mechanism exists besides the baroreceptor reflex. This rapidly responding system acts at the site of the vasculature. Changes in arterial blood pressure lead to corresponding changes in vascular shear stress. This mechanical stimulus activates nitric oxide synthase (eNOS). The subsequently formed nitric oxide (NO) diffuses into the adjacent vascular smooth muscle cells decreasing the vascular resistance and blood pressure is maintained at its initial level. The vascular NO system is most effective in dampening blood pressure fluctuations.

There is extensive evidence that the kidneys dominate in long-term control of arterial pressure by altering body fluid volume through pressure natriuresis, the ability of the kidneys to respond to changes in arterial pressure by altering the renal excretion of salt and water. Sympathetic nervous system play an important role in regulating renal blood flow, glomerular filtration rate, renin release, and urinary sodium and water excretion (Hartner A et al. 2003).

The sympathetic nervous system has moved towards the center stage in cardiovascular medicine. The classical concept from Cuyton of the renal fluid feedback mechanism for long-term control of arterial pressure has been challenged by a new theory (Korner PI 2007) arguing strongly for a primary role of the CNS and SNA in the regulation of blood pressure through total peripheral resistance, and development of hypertension (Castrop H et al. 2010). According to this theory, alterations in peripheral resistance and cardiac function lead to chronic changes in arterial pressure while kidney function somehow spontaneously adapts to pressure changes allowing for achievement of sodium balance (Bie P 2009, Osborn JW et al. 2009, Seelinger E et al. 2004).

2.2 Elevated blood pressure (hypertension)

2.2.1 General

Blood pressure (BP) is a biological variable with no cut-off point separating normotension from hypertension. The continuous relationship between BP and the risk of CV and renal events makes the distinction between normotension and hypertension difficult. Thus, a definition of hypertension is somewhat arbitrary. In practice, cut-off BP values are universally used, both to simplify the diagnostic approach and to facilitate the decision about treatment. According to the ESH/ESC guidelines, hypertension is defined as values ≥ 140 mmHg SBP and/or ≥ 90 mmHg DBP, based on the evidence from randomized controlled trials (RCTs) demonstrating that in patients with these BP values treatment-induced BP reductions are beneficial. One cut-off point is the level of arterial blood pressure with doubling of long-term cardiovascular risk (Manchia G et al. 2013). In a cohort study of more than 1.2 million Swedish young men with up to 37 years of follow-up, the relation of diastolic blood pressure to mortality was monotonic and positive, with an apparent risk threshold around a pressure of about 90 mmHg. The relation of

systolic blood pressure to mortality was U-shaped, with the lowest risk at a pressure of about 130 mmHg. The relations of both blood pressures to cardiovascular mortality were positive and monotonic, but their relations to non-cardiovascular mortality were driven by inverse relations of systolic blood pressure to risk of death from external causes (Sundström J et al. 2011).

Hypertension is the most important risk factor for stroke and with abnormal lipids and smoking the most important risk factor for myocardial infarction worldwide (O'Donnell MJ et al. 2010). It has been estimated that globally 13.5% of all deaths are attributed to high blood pressure and hypertension accounted for 35% of all annual deaths in Europe (Lawes CMM et al. 2008). In Finland, 41% of men and 22% of women had at least mildly elevated blood pressure (BP $\geq 140/90$ mmHg). Moderately elevated BP (BP $\geq 160/100$ mmHg) was observed in 10 % of men and 4 % of women (Laatikainen T et al. 2012).

It has often been reported that “the causes of hypertension are unknown,” but this opinion denies the fact that an enormous number of papers have been published on the etiology of hypertension. The multifactorial nature of the disease means, however, that it is hard to bring the vast array of information into a cohesive framework.

2.2.2 Obesity

Up to 70% of newly diagnosed cases of hypertension are attributable to obesity (Moore LL et al. 2005). Excess weight gain is associated with SNS activation, which contributes to renal sodium retention and impaired pressure natriuresis. However, not all obese individuals are hypertensive, although the prevalence of hypertension is higher in obese than in lean populations. Excess weight gain shifts the distribution of blood pressure towards higher values. Thus, obese individuals not classified as being hypertensive would have lower BP at a lower body weight (Alwan A 2011, World health statistics 2012). This concept is supported by the nearly linear relationship between BMI and BP, by the fact that excess weight gain, especially when accompanied by increased visceral adiposity, predicts future development of hypertension (CDC 2012), and that weight loss helps to prevent the development of hypertension and reduces BP in most hypertensive individuals (Weinberger MH et al. 2001).

2.2.3 Heritability

There is evidence for strong heritability of many cardiovascular risk factors including hypertension, although family history is a variable combination of genetics and shared environment. The heritable component of BP has been documented in family and twin studies suggesting that 30–50% of the variance of BP readings is attributable to genetic

heritability and about 50% to environmental factors (Tarnoki AD et al. 2012, Salomaa V 2014).

2.2.4 Salt sensitivity

The salt sensitivity plays an important role in patients with essential hypertension, although in statistics of essential hypertension the salt-sensitive hypertension is not distinguished from salt-resistant hypertension. This distinction would be important because salt sensitivity, independent of blood pressure, is a risk factor for cardiovascular morbidity and mortality and other diseases (Felder RA et al. 2013).

2.2.5 Alcohol

Heavy intake of alcoholic beverages increases BP, but light to moderate alcohol intake is probably unrelated to increased BP (Klatsky AL and Gunderson E 2008), although recent studies show a consistent linear dose–response associations between alcohol consumption and incident hypertension (Okubo Y et al. 2014, Peng M et al. 2013). The mechanisms remain unclear, but repetitive alcohol-related sympathetic activation may play a permissive role in development of both functional and structural cardiovascular changes, and consequently may lead to chronic hypertension (Hering D et al. 2011). The patterns and frequency of drinking among low-risk drinkers seems to be important. Those who drink more regularly show a lower risk of CHD than those who drink infrequently, even among low average alcohol drinkers or when alcohol volume has been taken into account (Tolstrup J et al. 2006). It is likely that regular light drinkers have advantageous life-style characteristics compared to infrequent light drinkers or binge drinkers. There are no RCTs of moderate alcohol drinking with CAD or other end points. Residual unmeasured confounding factors could be playing a role in the benefits associated with light to moderate drinking in observational studies.

2.2.6 Tracking

Often the essential hypertension has its origins in the youth. There is a substantial body of epidemiologic data that link higher BP levels in childhood with early onset hypertension in the adulthood (Falkner B 2012). Cohort studies that obtained repeated measures of BP from childhood into young adulthood describe tracking of blood pressure, with higher BP levels in childhood corresponding with higher BP levels in young adulthood. The BP tracking phenomenon was confirmed by Chen and Wang (Chen X and Wang

Y 2008) in their meta-analysis on 50 published cohort studies, representing diverse populations.

The definition of hypertension in childhood is, however, complicated. It is based on a body of normative data and the upper 5% of the normal BP distribution is defined as hypertensive. Due to high variability in BP measurement in children at least three separate measurement periods are needed (Redwine KM and Falkner B 2012). In addition, there is a strong association of obesity with high BP in both children and adolescents (McNiece KL et al. 2007, Acosta AA et al. 2012). The prediction of hypertension in adulthood can be improved significantly by using data on childhood overweight or obesity connected with parental hypertension history, family socioeconomic circumstances and genetic markers (Juhola J et al. 2012).

2.2.7 Pregnancy

Hypertension during pregnancy is associated with a higher risk of subsequent arterial hypertension, even in the absence of risk factors such as obesity (Daviglius ML et al. 2004). As a physiological “stress test”, pregnancy may uncover susceptibility to subsequent chronic disease, particularly of a vascular or metabolic origin. In the Northern Finland Birth Cohort Study (Männistö T et al. 2013) elevated BP during pregnancy was observed in ≈17% of all patients and ≈30% of them had a cardiovascular event before their late 60s and 3% died of MI. All women who had transient hypertension during pregnancy were at higher risk (64% to 153%) of developing chronic hypertension. The precise relationship between hypertensive disorders of pregnancy and later onset of hypertension remains incompletely resolved. One possibility is that the hypertension in pregnancy and preeclampsia in particular, leaves permanent vascular and inflammatory changes that increase the risk for hypertension and CVD later in life. Notably, 60% of reproductive-aged women have ≥1 cardiovascular risk factor, which is associated with an increased cardiovascular disease risk during the life course (Daviglius ML et al. 2004, Pencina MU et al. 2009).

2.2.8 Biomarkers

There are a lot of biomarkers, which act as precursors of manifest hypertension. An adrenergic overdrive is documented in patients with hypertension, and the sympathetic activation is directly related to the severity of the hypertensive state (Grassi B 2009). Whether the heart rate itself is a risk factor for development of hypertension or just a marker for increased sympathetic activation is still a matter of debate (Tjugen TB et al. 2009). The hyperkinetic state has been defined as the clustering of elevated heart rate, norepinephrine levels (suggesting sympathetic overactivation), and cardiac output among

borderline hypertensive subjects (Tjogen TB et al. 2010). Sympathetic overactivation increases vasoconstriction of resistance vessels through adrenergic stimulation, resulting in increased BP (Jamerson KA et al. 1993, Jamerson KA et al. 1994).

Established phase of hypertension is associated with increased total peripheral resistance, normal cardiac output with normalization of sympathetic tone. The plasma norepinephrine levels have also been normalized in many studies after transition to established hypertension.

Impaired endothelial function is associated with manifest hypertension and undergoes rapid structural and functional changes that finally result in impaired vasorelaxation, oxidative stress and increased adhesiveness of circulating leukocytes (Linder L et al. 1990, Panza JA et al. 1990). The temporal sequence and hence causality of the latter association is, however, uncertain (Taddei S et al. 1996, Paniagua OA et al. 2000). Results from longitudinal studies of endothelial dysfunction measured using the flow-mediated vasodilatation technique (FMD) and risk of development of hypertension are conflicting (Rossi R et al. 2004, Shimbo D et al. 2010). In Uppsala Seniors (PIVUS) study of elderly, impaired endothelial function measured with the invasive forearm technique (EVD) did not play a major role in the development of hypertension or blood pressure progression and the observed associations between endothelial dysfunction and risk of cardiovascular events are likely mediated through other pathways than hypertension (Lytsy P et al. 2013). Similarly, in a long-term analysis of the FATE study (Anderson TJ et al. 2011), FMD was not predictive of subsequent cardiovascular events and remained an insignificant predictor in addition to the Framingham risk score. In a recent study of Shechter (Shechter M et al. 2014) using the upper arm cuff occlusion for evaluating FMD found that brachial artery median FMD independently predicts long-term adverse CV events in healthy subjects with no apparent heart disease in addition to those derived from traditional risk factor assessment. The International Brachial Artery Reactivity Task Force (Corretti MC et al. 2002) has been unable to reach a consensus as to which technique provides the most accurate or precise data. Endothelial dysfunction has a key role in microvascular alterations and is closely but not specifically related to hypertension (Yannoutsos A et al. 2014).

2.3 Ankle blood pressure

The blood pressure waveform amplifies as it travels distally from the heart, resulting in a progressive increase in systolic blood pressure. The amplification is due to retrograde wave reflection from resistant distal arterioles, which is additive to the antegrade wave (Figure 1).

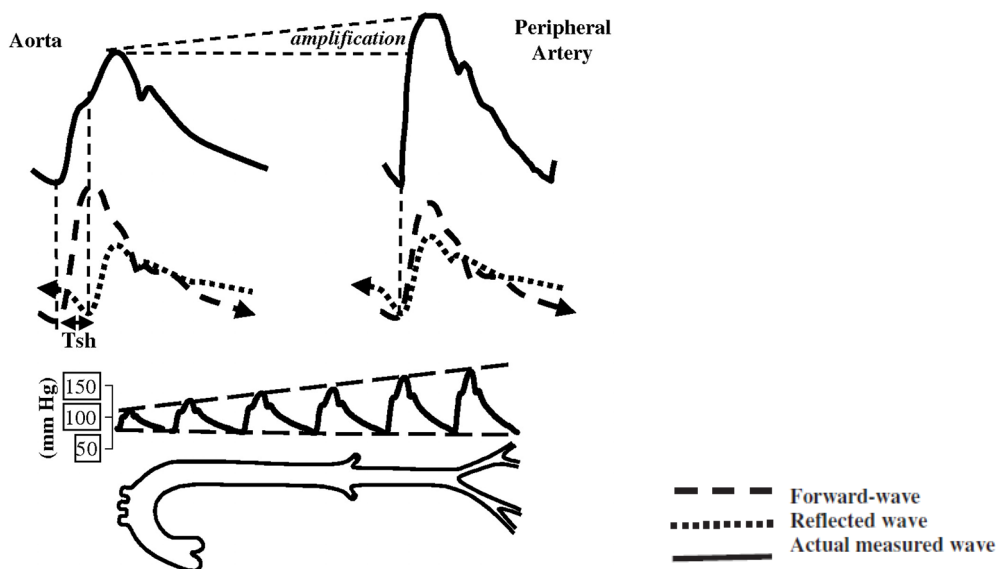


Figure 1. Schematic representation of arterial pressure waves travelling from the aorta towards the periphery and back. Reflected wave returns towards the aorta with a delay and therefore the aortic PP and systolic pressures are lower than in periphery. Redrawn from London et al.(2010)

In the lower extremities hydrostatic pressure causes increased intraluminal pressure, with increased wall thickening and with unchanged inner radius. Therefore, both reflected waves and changes in vessel wall thickness and consequently stiffness contribute to systolic blood pressure amplification (Aboyans A et al. 2012). Anaesthesiologists have investigated the suitability of alternative sites for blood pressure measurement in 100 awake healthy volunteers (Moore C et al. 2008). The ankle blood pressure was on average 8 mmHg higher than the arm BP. The 95% confidence intervals of agreement are, however, wide (-8.2 to 24.0) and it is suggested to take a single blood pressure reading at the arm before proceeding to use the ankle for ongoing blood pressure measurement. This gives an indication for a given patient of the degree of difference between the two sites, and allows appropriate interpretation of subsequent results (Moore C et al. 2008). The mean ankle-brachial index in normal children is 1.0, 1.1, and more than 1.1 in aged 1, 1.5, and 2 years with body surface areas of 0.4, 0.5 and 0.6 m², respectively (Katz S et al. 1997). In adults, the mean normal ABI is 1.15–1.17 (Smith FB et al. 2003, Zheng ZJ et al. 1997). There are no reference values for ankle blood pressure.

2.4 Elevated ankle blood pressure

As mentioned above the blood pressure amplifies as it travels distally. Elevated ankle blood pressure can be expected, when the systolic blood pressure is elevated or arteries are stiffer. An increased ankle blood pressure and high ABI index may also be expected with aging as a result of arterial stiffening. One important cause is the calcification of the arterial wall and may occur in ageing patients with medial calcinosis, diabetes mellitus, or end-stage renal disease. According to the recent American guidelines the ankle artery is incompressible (Monckeberg's sclerosis), when systolic pressure cannot be measured despite cuff inflation > 250 mmHg or the ABI index is over 1.40 (2011 ACCF/AHA Guidelines). When ankle BP is measured in clinical settings, it is exclusively used in the calculation of ankle-brachial pressure index for the diagnosis of peripheral arterial disease.

At present, there are no prospective follow-up studies, as to how elevated systolic blood pressure, arterial stiffness, medial calcinosis or occlusive stenotic changes alter the ankle blood pressure over time (Kain K et al. 2013). It has been postulated that raised ankle pressures due to arterial stiffness precede occlusive vascular disease in the lower limbs. Arterial stiffness in elastic arteries, but not in muscular arteries, increased significantly with advancing age and the presence of high plasma glucose and high BP (Zhang Y et al. 2013). Interestingly, in a recent population based study (Wohlfahrt P et al. 2013) the aortic stiffness was more related to ankle blood pressure and the elevated ankle blood pressure is more a parameter of aortic stiffness than lower-extremity arterial stiffness. In another recent study (Kain K et al. 2013) the higher ankle pressure without indexing to brachial pressures was one of the earliest signs of adverse changes in the arteries in South Asians with DM. Elevated aortic stiffness increases the transmission of pulsatile energy to the periphery and may be a potential mechanism explaining the association between ankle blood pressure and pulse wave velocity (PWV).

In an another recent study the mean ankle blood pressure was the strongest predictor of carotid augmentation index (AIx) among the BP recordings and this relation remained significant even when the influence of age, sex, race, height, heart rate, brachial MAP and brachial–ankle pulse wave velocity were statistically accounted for (Tarumi T et al. 2011) and the strength of the correlation was significantly stronger in younger persons than in the older men. These results suggest that peripheral vascular resistance of the lower body, as estimated by ankle MAP, contributes importantly to wave reflection and augmentation of central BP. On the other hand, elevated ankle blood pressure is measured due to more pulsatile energy.

2.5 High ankle-brachial index (high ABI)

A high ABI represents poorly compressible infra-popliteal vessels and is histologically associated with medial arterial calcification in diabetic patients (Everhart JE et al. 1988, Young MJ et al. 1993, Chantelau E et al. 1995). This process can mask the detection of PAD, and indeed a high ABI has been observed in tandem with lower extremity atherosclerosis in diabetic patients (Aboyans V et al. 2011a, Aboyans V et al. 2008a). However, elevated ABI does not simply appear to be “atherosclerosis masked”, as important differences in CVD risk factors and vascular outcomes exist between those with low and high ABI (Aboyans V et al. 2011b, Allison MA et al. 2008). In one recent study the survival in poorly compressible artery (PCA) patients was lower than in those with a normal ABI and even lower than in patients with PAD (Arain FA et al. 2012). The presence of abnormal Doppler in patients with PCA was associated with a significant increment in the risk of death, suggesting that concomitant atherosclerosis adds to the risk due to medial arterial calcification. High ABI is associated directly with male sex, diabetes mellitus, and hypertension but is inversely associated with smoking and hyperlipidemia (Aboyans V et al. 2008b, Allison MA et al. 2008). Allison (Allison MA et al. 2008) demonstrated that an ABI >1.40 was associated with stroke and congestive heart failure but not with myocardial infarction or angina. In MESA, high ABI was associated with incident CVD (Criqui MH et al. 2010). Other studies have reported inconsistent results (Sutton-Tyrrell K et al. 2008, Wattanakit K et al. 2007, Resnick HE and Foster GL 1999). Especially among diabetic patients high ABI bears a different relationship to traditional CVD risk factors than low ABI. They have a shorter history of tobacco use, are more likely Caucasian males with longer duration of diabetes. Also coronary artery calcification (CAC) is more prominent in high ABI diabetic patients (Lilly SM et al. 2013). In the general population increased CAC or carotid intima media thickness (cIMT) has not been reliably detected in patients with high ABI (McDermott MM et al. 2005, Signorelli SS et al. 2010). In one study (Ix JH et al. 2010) high ABI was strongly associated with greater LV mass in community-living persons without clinical CVD. This association was not materially altered when adjusted for subclinical atherosclerosis in nonperipheral arterial beds. It is obvious that in patients with high ABI the systolic BP and PP are elevated due to arterial stiffness and they have greater left ventricular mass (Arain FA et al. 2012, Ix JH et al. 2010).

In diabetes the medial arterial calcification (MAC) is common. In a cross-sectional study of 185 community-living individuals with mean age of 32 years and diabetes duration of 23 years, 57 % had MAC in the x-ray examination. Interestingly, the ankle-brachial pressure difference (ABD) >25 mmHg gave the best overall accuracy (70%) with sensitivity of 57% and specificity of 84%. Cut-points (ABI >1.4 or ABD >25 mmHg), suggested in the literature, provided high specificity but poor sensitivity (Ix JH et al. 2012). Those will probably identify individuals with severe or long-standing MAC.

2.6 Low ankle-brachial index (low ABI)

The low ABI is the diagnostic tool most commonly used to define peripheral artery disease (PAD). Lower extremity peripheral artery disease is the third leading cause of atherosclerotic cardiovascular morbidity, following coronary artery disease and stroke (Fowkes et al. 2013). It is recognized as a clinically important marker of atherosclerotic disease due to its strong association with cardiovascular disease incidence and mortality (Fowkes et al. 2013, Selvin E et al. 2004, Newman AB et al. 1999). In a large-scale prospective study 1 in 5 elderly patients visiting their primary care physician had PAD (12.2% asymptomatic, 8.7% symptomatic) (Hirsch AT et al. 2001). It provides additional information on risk beyond the assessment of conventional risk factors.

There is controversy about what ABI threshold should be used to diagnose PAD. An ABI ≤ 0.90 remains the most common threshold to detect $>50\%$ stenosis identified by imaging methods or angiography (Diehm C et al. 2009, Wilkinson IB et al. 2000, Allen J et al. 1996, Niazi K et al. 2006, Premalatha G et al. 2002, Schroder F et al. 2006, Williams DT et al. 2005). All these studies found reasonably high specificity (83%–99%) but lower sensitivity (69%–79%). According to Bayes' theorem the probability of ABI should also be interpreted according to the a priori probability of PAD in the population studied.

2.7 Criticism about ABI measurement

The current lack of standards for measurement and calculation of the ABI leads to discrepant results with significant impact from clinical, public health, and economic standpoints (Aboyans A et al. 2012). In a review of 100 randomly selected reports using the ABI, multiple variations in technique were identified, including the position of the patient during measurement, the sizes of the arm and leg cuffs, the location of the cuff on the extremity, the method of pulse detection over the brachial artery and at the ankles, whether the arm and ankle pressures were measured bilaterally, which ankle pulses were used, and whether a single or replicate measures were obtained (Klein S and Hage JJ 2006).

The ABI measurement had a high specificity but low sensitivity for PAD (Guo X et al. 2008, Dachun X et al. 2010). The ABI varies according to the population studied, the cutoff threshold, and the technique used to detect flow in the ankle arteries. The accuracy of the ABI is generally based on severe cases of PAD and data on the optimal ABI threshold for the diagnosis of PAD are scarce.

The relatively low sensitivity is due to several reasons: mild peripheral artery disease might not be detected by ABI at rest because severe stenosis in at least one major artery is needed to reduce the ankle pressure. On the other hand, lesions affecting the internal

iliac or the femoral profunda arteries, as well as distal peripheral artery disease in the pedal or toe arteries, do not affect the ABI.

Medial vascular calcification (Monckeberg's sclerosis) and intimal stenotic lesions (atherosclerotic) frequently coexist, especially with ageing, diabetes mellitus or end-stage renal disease. When vascular calcification is present, stenotic occlusive disease cannot be reliably detected by the ABI (Suominen V et al. 2008, Aboyans V et al. 2008). In a recent Chinese study, increased interankle BP differences detected mild arterial disease in the lower extremities better than ABI (Sheng CS et al. 2013).

According to a recent statement the Doppler method should be used for the determination of the ABI (gold standard) (Aboyans A et al. 2012). In many large-scale studies, however, oscillometric methods have been used. The oscillometric technique is based on the assumption that the maximum oscillations appearing during cuff deflation correspond to the mean arterial pressure and that SBP and diastolic blood pressure can be calculated from the mean arterial pressure with mathematical algorithms. The devices have been designed for measuring blood pressure in non-obstructed arms, not the legs, and especially not in diseased legs (Jönsson B et al. 2001, Ramanathan A et al. 2003, Beckman JA et al. 2006, Mehlsen J et al. 2008, Aboyans V et al. 2009). Many studies have questioned the validity of the oscillometric method for the detection of PAD. The correlation between Doppler-derived and oscillometry-determined ankle pressures and ABIs in healthy subjects or subjects with mild PAD have been acceptable.

When the ABI determined by the Doppler method is in the low range, the oscillometric method results in an overestimation of the actual pressure or is unable to detect low pressures (Aboyans A et al. 2012, Korno M et al. 2009, Nukumizu Y et al. 2007, Ramanathan A et al. 2003).

The toe vessels are less susceptible to vessel stiffness and the determination of toe-brachial index (TBI) may be useful. The TBI had a sensitivity of 90% to 100% and a specificity of 65% to 100% for the detection of vessel stenosis (Høyer C et al. 2013). No firm conclusions could be drawn about the role of TBI as a prognostic marker for cardiovascular mortality and morbidity. In contrast to the well-defined and evidence-based limits of the ABI, the diagnostic criteria for a pathologic TBI remain ambiguous and a TBI <0.70 as the cutoff value is not strictly evidence-based (Høyer C et al. 2013). In one Finnish study 28% of those with low ABI did not have abnormal TBI and at the same time 27% of those with normal ABI had abnormal TBI. Reason for this discrepancy might be in the validity on oscillometric devices and also significant PAD in calcified vessels (Suominen V et al. 2010).

2.8 Central blood pressure and arterial stiffness

2.8.1 General

In young people with normal viscoelastic properties of large artery wall, backward and forward waves meet in the ascending aorta at the end of systole, and the superimposition of these two waves occurs throughout the whole diastolic phase. The central SBP is, therefore, mainly defined by the forward pulse wave magnitude, i.e. interaction of left ventricular ejection with the impedance of the circulation. The backward waves are also attenuated due to the windkessel effect. The natural elasticity of the aorta buffers large changes in pulse pressure due to ventricular ejection, ensuring that vital organs do not receive damagingly high pulsatile blood flow.

The aging of the large arteries is characterized by progressive collagen accumulation and changes in the structure of elastic lamellae, which become sparse, disorganized and fractured (O'Rourke MF and Hashimoto J 2013). The net effect of arterial remodeling associated with aging is a progressive reduction in vascular elasticity and compliance. The peripheral and central systolic blood pressure increase, whereas diastolic blood pressure decreases and the mean arterial pressure remain constant.

'A man is as old as his arteries' (Leonard A 1990). This aphorism is based on the observations that arterial ageing and cardiovascular risk such as hypertension, obesity, impaired glucose tolerance, and dyslipidemia (Sutton-Tyrrell K et al. 2001, Männistö T et al. 2013, Mitchell GF et al. 2007) are associated with increased arterial stiffness and elevated pulse pressure (Yambe M et al. 2007, Kaess BM et al. 2012). Increased arterial stiffness in the large elastic arteries leads to an increase in central blood pressure (BP) and ultimately to target organ damage (Kotsis V et al. 2011, Safar ME et al. 2012), particularly in high flow organs such as the heart, kidneys and brain.

2.8.2 Arterial stiffness

Arterial stiffness can be considered as a measure of the cumulative influence of cardiovascular risk factors with aging on the arterial tree. It reflects true arterial wall damage. In contrast to the classical 'circulating' cardiovascular risk factors, such as BP, glycaemia and lipids, arterial stiffness integrates the long-lasting effects of all identified and nonidentified cardiovascular risk factors and thus may be considered as a 'tissue' biomarker.

Arterial stiffness, assessed by PWV, significantly and progressively increases with age in elastic arteries in both men and women, whereas in muscular arteries, only slight age-related modifications in PWVs have been detected in men (Zhang Y et al. 2013). Only in elastic arteries, but not in muscular arteries, PWV was significantly and independently associated with plasma glucose, brachial BPs and carotid IMT (Selvin E et al. 2004).

It is attributable to the elastin depletion and collagen deposition in elastic arteries with advancing age. Thus, compared with elastic arterial stiffness, the stiffness in muscular arteries seems to be ‘invulnerable’ to conventional cardiovascular risk factors, including age, smoking, plasma glucose and cholesterol, BP levels and arterial wall thickness.

Increased arterial stiffness in the large elastic arteries leads to an increase in central blood pressure. The amplitude of forward wave increases, pulse wave propagates faster and backward wave returns earlier and stronger because the elasticity of vessels is diminished. A premature return of reflected waves in late systole increases central systolic and pulse pressure with more loads on the left ventricle enhancing myocardial oxygen demand. On the other hand, the increased arterial stiffness in elastic arteries and unchanged arterial stiffness in muscular arteries would contribute to an attenuated mismatch between central aorta and peripheral arteries, and consequently lead to an increase in pulsatile energy transmitted from the aorta to the microcirculation (Mitchell FG 2008).

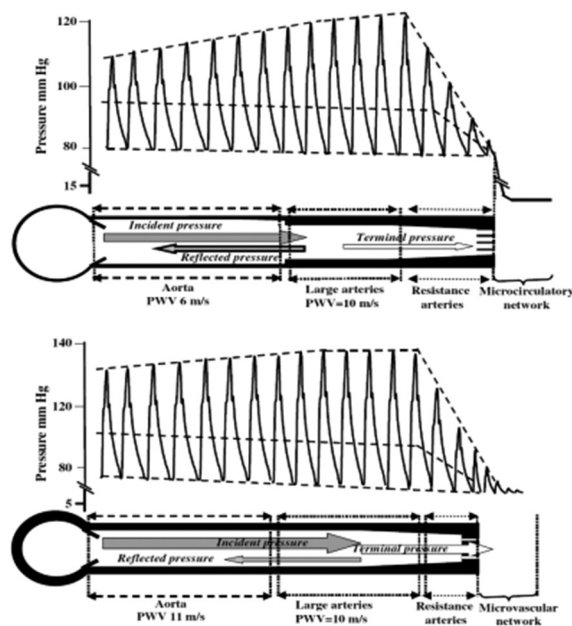


Figure 2. Upper panel. In the presence of normal arterial stiffness the reflections occur distant from microcirculation. The reflected wave returns to the aorta in diastole maintaining normal aortic pulse pressure. The windkessel effect together with the partial reflections limit the transmission of pulsatile pressure energy to the periphery and protect the microcirculation. Lower panel. Elevated aortic stiffness. Elevated aortic pulse pressure. Due to an attenuated mismatch between central aorta and peripheral arteries pulsatile pressure is not sufficiently dampened and is transmitted and damaging the microcirculation. Redrawn from London et al. (2010)

The arterial stiffness has good predictive value for cardiovascular events, independent of conventional cardiovascular risk factors (Manchia G et al. 2013). It is regarded as a direct measure of target organ damage, indicating the occurrence of pathological changes in large artery walls under the action of cardiovascular risk factors. Several cross-sectional studies have assessed factors associated with higher arterial stiffness. High blood pressure, diabetes, heart rate, and to a lesser degree presence of dyslipidemia, and smoking, have been reported to be independently associated with greater arterial stiffness (Yambe M et al. 2007, Takase H et al. 2011, Benetos A et al. 2002, Sa Cunha R et al. 1997, Wang F et al. 2011, Stefanadis C et al. 1997). Also in a population-based sample of middle-aged men the aortic stiffness had a significant positive association with aortic calcification measured as aortic calcium score, suggesting that aortic calcification is one mechanism responsible for aortic stiffness in middle-aged men (Sekikawa A et al. 2012).

Prospective studies have suggested that the vascular stiffness is more likely a precursor than the result of hypertension. Higher arterial stiffness was predictive of incident hypertension, whereas higher initial blood pressure was not predictive of an increase in arterial stiffness (Kaess BM et al. 2012). In the Baltimore Longitudinal Study of Aging (Najjar SS et al. 2008) increased arterial stiffness in nonhypertensive persons predicted later incidence of hypertension. Elevated aortic blood pressure with normal or high-normal brachial blood pressure identified those patients with target organ changes (Booyesen HL et al. 2013). Elevated blood pressure during pregnancy as a stressor signals higher risk of cardiovascular, cerebrovascular, and kidney disorders, as well as diabetes mellitus, later in life (Männistö T et al. 2013). In summary, it seems that that arterial stiffness begins to manifest at the very early stage of hypertension, even before prehypertension. Vascular stiffness is likely to be a precursor rather than the result of hypertension (Kaess BM et al. 2012).

2.8.3 Measurement

Arterial stiffness can be measured by pulse wave velocity (PWV) or augmentation index (AIx). The former measures the speed of travel of the pulse wave in the aorta. AIx is the pressure increment from the shoulder of the systolic waveform. The AIx quantifies the role of wave reflection in determining an elevation of central blood pressure.

The PWV is generally accepted as the most simple, non-invasive, robust and reproducible method to determine arterial stiffness. The relationship between aortic stiffness and CV events is continuous, but a threshold >12 m/s has been accepted as an estimate of significant alterations of aortic function in middle-aged hypertensive individuals (Manchia G et al. 2007). European Society of Cardiology (ESC) guidelines for the management of arterial hypertension include PWV in a list of factors influencing the prognosis of patients with hypertension and recommend a threshold PWV value of greater than 12 m/s to be used as an index of large artery stiffening and an indicator of

sub-clinical organ damage (Mancia G et al. 2007). In the Rotterdam Study the aortic PWV was a strong predictor of coronary heart disease and stroke and improved the prediction of CVD when added to known conventional risk factors (Mattace-Rasso FUS et al. 2006).

There are two possible mechanisms for the PWV increase. The first one is due to structural, and the other one due to functional changes of arterial wall. Structural stiffening of elastic arteries caused by aging and other cardiovascular risk factors is explained by fragmentation and alteration of the elastic fiber network responsible for the buffering function of arteries (Laurent S et al. 2005). Functional stiffening of arteries results from increased blood pressure. Under normal blood pressure, elastic elastin fibers are recruited. Increased blood pressure loads stiffer collagen fibers, thereby increasing arterial stiffness. This explains the nonlinear relationship between blood pressure and PWV (Wagenseil JE and Mecham RP 2009). Functional stiffening of arteries can be reversed by blood pressure lowering (Asmar RG et al. 1988). In the presence of structural changes, the stiffening is less dependent on blood pressure (Mourad JJ et al. 1997). The PWV increase due to structural changes is more deleterious than the functional PWV increase caused by increased blood pressure (Wohlfahrt P et al. 2013). In summary, the association between vascular stiffening and blood pressure is particularly interesting because the functional relationship is likely bidirectional (Yannoutsos A et al. 2014). Elevated blood pressure may cause vascular damage and accelerated conduit artery stiffening. Conversely, aortic stiffening increases pressure pulsatility and therefore affects systolic blood pressure. Temporal relationships between vascular stiffness and blood pressure remain, however, incompletely elucidated.

2.8.4 Central haemodynamics

The predictive value of central haemodynamics is based on its pathophysiological importance. It is aortic systolic pressure that the left ventricle encounters (“sees”) during systole (afterload) and the aortic pressure during diastole is a determinant of coronary perfusion.

Central pulse pressure (cPP) can be partitioned into the height of the first shoulder of the central pulse wave (P1) and augmentation pressure or index (AP, Aix). P1 is determined by stroke volume and by the impedance of the aorta. AP is thought to be determined by pressure wave reflection from the periphery and/or by the functional compliance or “reservoir function” of the aorta (Davies JE et al. 2010, Van Bortel LM et al. 2011). It has generally been regarded as a measure of pressure wave reflection influenced by the tapering of the arterial tree and hence by arterial tone in muscular arteries (Cecelja M et al. 2012).

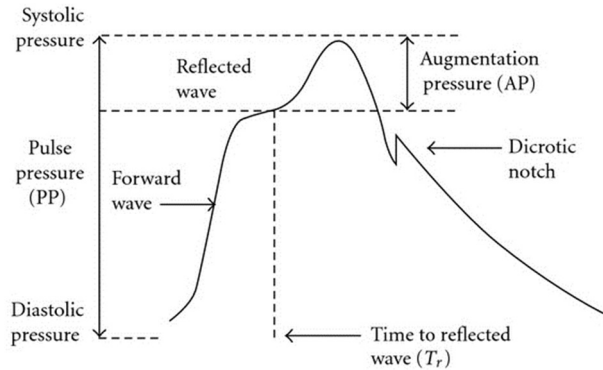


Figure 3. Central (aortic) pulse pressure and augmentation pressure

Figure 3. Aortic pulse pressure waveform. Augmentation pressure is the additional pressure added to the forward wave by the reflected wave. Augmentation index is defined as the augmentation pressure as a percentage of pulse pressure. The dicrotic notch represents closure of the aortic valve and is used to calculate ejection duration. Time to reflection is calculated as the time at the onset of the ejected pulse waveform to the onset of the reflected wave.

Interestingly, compared with P1, AP bears little relation to aortic stiffness and can be influenced by nitrovasodilation independently of any effect on aortic stiffness (Van Bortel LM et al. 2011, Cecelja M et al. 2009, Kelly RP et al. 2001). Also AP is independent of the intrinsic stiffness of the arterial wall as measured by using PWV (Cecelja M et al. 2012, Cecelja M et al. 2009). The differing age-related changes in AP and P1 explain the nonlinear increase in aortic stiffening with age (Kelly RP et al. 2001, McEniery CM et al. 2005). In young individuals the amplification of cPP is mainly determined by AP, in older age with stiffer aorta the P1 widening is seen in the reduced progression of augmentation index (Aix). The stiffer aorta with increased incident wave magnitude is then the main important determinant of both cPP and peripheral pulse pressure (Mitchell GF et al. 2010). Due to the variable degree of amplification of the pulse pressure wave from the aortic root to the peripheral circulation the brachial pressure is not a perfect surrogate for central aortic pressure. The amplification process is influenced by many factors, including ageing and aortic stiffness, heart rate, height or gender.

It seems that the cPP, Aix and PWV are jointly associated with future systolic blood pressure and incident hypertension. Further, elevated aortic forward amplitude and augmentation index seem to correlate better with incident hypertension than cfPWV (Kaess BM et al. 2012, Tomiyama H et al. 2013).

Arterial stiffness is positively, but nonlinearly related to distending pressure and the augmentation of reflected wave is perhaps one of the earliest signs of vascular damage. While PWV reflects more the viscoelastic properties of the aorta and Aix is more an indicator of the reflected waves, it seems to be reasonable to differentiate between PWV

and Aix. However, these two factors are interrelated as increased arterial stiffness can be measured by both PWV and Aix.

The discrepancy in arterial stiffness between elastic and muscular arteries would probably lead to an attenuated impedance match between aorta and peripheral arteries and future microcirculation-related end-organ damage (Zhang Y et al. 2013). There is a cross-talk between the microcirculation and the macrocirculation (Laurent S et al. 2009) to promote a vicious circle of increased peripheral vascular resistance with increased arterial stiffness in the large elastic arteries leading to an increase in central blood pressure. These pathophysiological abnormalities are directly related to the development of hypertension via abnormal pressure wave reflection/microvascular damage in the peripheral arteries caused by increased propagation of pressure energy (Tomiyaama H and Yamashina A 2012, O'Rourke MF et al. 2010, Tomiyama H and Yamashina A 2010, Yambe M et al. 2007, Kaess BM et al. 2012, Najjar SS et al. 2008, Takase H et al. 2011), which accelerates the decline of renal function via pulsatile nephropathy. On the other hand, renal dysfunction is thought to be related to the development of hypertension via impairment of renal sodium and water excretion and/or enhancement of the renal sympathetic nerve activity (Takase H et al. 2012, Gross ML et al. 2005).

2.9 Exercise blood pressure and exaggerated exercise blood pressure

2.9.1 General

During normal exercise, cardiac output increases in response to the demand of working muscles because of a sympathetically mediated increase in heart rate and stroke volume. Arterial pressure, both peripheral and central, rises in a graded fashion with increasing exercise intensity. Systemic vasodilatation offsets the rise in cardiac contractility, heart rate, and left ventricular output, resulting in increased peripheral blood flow (Sharman JE et al. 2005). Increased cardiac output, decreased peripheral vascular resistance, and their interactions determine blood pressure during exercise.

When cardiac output is not balanced by increased compliance from peripheral muscle vasculature dilation, the result is a sharp increase in systolic blood pressure. Also vascular stiffness or an exaggerated sympathetic response on exercise might promote exaggerated blood pressure reaction, although the relative contributions of increased vascular stiffness or impaired endothelial function to exercise have not been evaluated in a large community-based sample.

The mechanisms underlying an excessive increase in systolic blood pressure are likely to be multifactorial. Structural abnormalities in the peripheral vasculature or an inability of the peripheral vasculature to appropriately vasodilate and allow peripheral runoff of increased blood flow, could increase BP during exercise (Fagard RH et al. 1996, Fossum E et al. 1999). One possible causative factor is the stiffening of large arteries that occurs

with the aging process which is accelerated in disease states (Laurent S et al. 2006). Third, impaired endothelial function may be associated with exaggerated blood pressure reaction (Tzemos N et al. 2009, Stewart KJ et al. 2004). Additionally, increased levels of serum cholesterol and insulin resistance have been shown to positively correlate with changes in BP with exercise (Brett SE et al. 2000, Gaudreault V et al. 2013). Physical fitness may also be an important factor, because it is related to insulin resistance and exercise BP responses (Fossum E et al. 1999).

The aortic pressure is the sum of a reservoir pressure and excess pressure caused by forward and backward propagating waves (Davies JE et al. 2007, Wang JJ et al. 2003). The exercise causes a systemic vasodilatation and backward wave augmentation is reduced (Munir S et al. 2008). The augmentation of central BP during exercise takes place mainly because of increases in forward propagating waves generated by left ventricular ejection. These incident waves are thus the principal components of excess pressure load induced with exercise and there seems to be only a minor role for wave reflection in exercise central BP (Schultz MG et al. 2013). In some studies the central to peripheral pressure amplification have been observed to magnify during exercise (Kroeker EJ and Wood EH 1955, Rowell LB et al. 1968). In summary, a reduction in aortic compliance together with structural abnormalities in the peripheral vasculature and an inability of the peripheral vasculature to appropriately vasodilate could increase BP during exercise (Fagard RH et al. 1996, Fossum E et al. 1999).

2.9.2 Cross-sectional and follow-up studies

Several cross-sectional studies have assessed factors associated with exaggerated BP response to exercise. In the recent report of the Framingham Offspring Study (Thanassoulis G et al. 2012) increased arterial stiffness and impaired endothelial function correlated significantly with higher exercise systolic BP response. Sung J et al. (2012) found similar results among volunteers for a health screening program. According to Tsiachris (Tsiachris D et al. 2010) exaggerated blood pressure response during exercise constitutes a sign of premature cardiovascular stiffening in the setting of uncomplicated hypertension. Some other studies have shown impaired endothelial function to be associated with an exaggerated BP response to exercise (Laurent S et al. 2006, Tzemos N et al. 2009).

In follow-up studies the prognostic value of an exaggerated exercise systolic blood pressure response remains, however, controversial. In the study of Weiss (Weiss et al. 2010) asymptomatic individuals with elevated exercise BP carried higher risk of CVD death but the result became nonsignificant after accounting for resting BP. However, Bruce stage 2 BP >180/90 mm Hg identified nonhypertensive individuals at higher risk of CVD death. In a recently published meta-analysis (Schultz MG et al. 2013) a

hypertensive response to exercise at a moderate exercise workload predicts CV outcomes independently of office BP, age, or multiple CV risk factors.

Bouzas-Mosquera (Bouzas-Mosquera et al. 2010) found, however, that a hypertensive response to exercise was associated with improved long-term survival and a lower risk of death or nonfatal MI in patients with DM and known or suspected CAD. The mechanism accounting for the more favorable outcome in this selected diabetic group might be related to the fact that an exercise-induced increase in cardiac output is a major determinant of the BP response during exercise and exaggerated exercise blood pressure might reflect a greater cardiac output reserve with high systemic vascular resistance. Also Campbell (Campbell et al. 1999) found that exercise hypertension is associated with a lower likelihood of myocardial perfusion abnormalities and is not associated with an increased mortality rate.

The results on the prognostic significance of exercise BP are not consistent (Smith RG et al. 2009), which may be due to the fact that the two haemodynamic components of BP change in opposite directions during a dynamic exercise: systemic vascular resistance decreases whereas cardiac output increases. Bottom line is the population studied. In population-based studies individuals with a hypertensive response to exercise likely have impaired vascular function, a blunted reduction of systemic vascular resistance during exercise , which limits their ability to compensate for the increased cardiac output. Such individuals may have normal (or near-normal) resting BP but the frequent transient increases in BP at low to moderate exercise may increase the propensity for developing LVH and may increase the risk for future cardiovascular disease events (Fagard RH et al. 1996).

On the other hand, when hypertension is associated with cardiac dysfunction and blunted exercise-induced increase of cardiac output, the prognostic significance of exercise BP may be lost (Fagard RH et al. 1996). A higher BP during exercise may even carry a better prognosis, in patients with suspected cardiac disease, or with heart failure, in whom a higher exercise BP implies relatively preserved systolic cardiac function (Smith RG et al. 2009, Hedberg P et al. 2009, Gupta MP et al. 2007, Corra U et al. 2012). In older patients with concomitant chronic diseases the impaired arterial dilatation translated into an excessive rise of BP may at least partly depend on cardiac output.

2.9.3 Consensus

According to the 2013 ESH/ESC guidelines on hypertension (2013) there is currently no consensus on normal BP response during dynamic exercise testing. One definition of an exaggerated BP response to exercise is considered as the systolic blood pressure ≥ 210 mmHg for men and ≥ 190 mmHg for women (Le VV et al. 2008, Smith RG et al. 2009). Other studies use the increase of SBP at fixed submaximal exercise (Le VV et al. 2008, Smith RG et al. 2009, Huot M et al. 2011, Sung J et al. 2012).

Exercise testing to predict future hypertension is not recommended because of a number of limitations, such as lack of standardization of methodology. Furthermore, there is no unanimity on the association of exercise BP with subclinical organ damage, such as LVH, after adjustment for other covariates, as well in normotensive as in hypertensive patients (Le VV et al. 2008). Also the predictive value of a hypertensive response for subsequent cardiovascular events seems to be low (Campbell L et al. 1999). There are, however, other studies, which show that a hypertensive response to exercise independently predicts cardiovascular events and mortality (Schultz MG et al. 2013, Skretteberg et al. 2013). It is associated with arterial stiffness in a normotensive population without clinical cardiovascular diseases (Sung J et al. 2012). In normotensive subjects and in mildly hypertensive patients with adequate increase of cardiac output, an exaggerated BP response predicts a poorer longterm outcome (Smith RG et al. 2009, Holmqvist et al. 2012, Sharman JE et al. 2011).

3 SUBCLINICAL TARGET ORGAN DAMAGE (OD)

3.1 General

Owing to the importance of asymptomatic OD as an intermediate stage in the continuum of vascular disease, and as a determinant of overall CV risk, signs of organ involvement should be sought carefully by appropriate techniques if indicated (2013 ESH/ESC Guidelines). A large body of evidence is now available on the crucial role of asymptomatic OD in determining the CV risk of individuals with and without high BP. The most important subclinical organ damages are seen in microalbuminuria, increased pulse wave velocity (PWV), left ventricular hypertrophy (LVH) and intima media thickness and/or carotid plaques (Yeboah J et al. 2012). Each of them can predict CV mortality independently of SCORE stratification and the risk increases as the number of damaged organs increases (Sehestedt T et al. 2010, Segestedt T et al. 2012, Volpe M et al. 2012).

3.2 ECG

A 12-lead ECG has a low sensitivity in detecting anatomic LVH but remains a valuable tool for the detection of hypertensive target organ damage and is an independent predictor of CV events (Levy D et al. 1994). It can be used to detect LVH, ventricular overload or 'strain', ischaemia, conduction abnormalities, left atrial dilatation and arrhythmias, including atrial fibrillation. Twenty-four-hour Holter electrocardiography is indicated when arrhythmias and possible ischaemic episodes are suspected. Atrial fibrillation is a very frequent and common cause of CV complications, especially stroke, in hypertensive patients (Kirchhof P et al. 2011).

3.3 Echocardiography

Echocardiography is more sensitive than electrocardiography in diagnosing LVH. It may help in a more precise stratification of overall risk and in determining therapy (Cuspidi C et al. 2002). Hypertension is associated with alterations of LV relaxation and filling (diastolic dysfunction). The Doppler transmitral inflow pattern can quantify filling

abnormalities and predict subsequent heart failure and all cause mortality (Aurigemma GP et al. 2001, Bella JN et al. 2002). Determination of left atrial dilatation can provide additional information and it predicts independently death, heart failure, atrial fibrillation and ischaemic stroke (Abhayaratna WP et al. 2006). In clinical practice, the routine execution of echocardiographic examination is expensive and not always available. Hypertensive patients with normal ECG and without other pathological conditions should not receive an echocardiographic examination routinely (Nardi E et al. 2012). However, the echocardiography in hypertensive patients at moderate CV risk may refine the risk evaluation by detecting LVH undetected by ECG and in hypertensive patients with ECG evidence of LVH it may more precisely assess the hypertrophy quantitatively.

3.4 Intima media thickness

Ultrasound examination of the carotid arteries with measurement of intima media thickness (cIMT) and/or the presence of plaques has been shown to predict the occurrence of both stroke and myocardial infarction, independently of traditional CV risk factors (Sehestedt T et al. 2010, Nambi V et al. 2010, Zanchetti A et al. 2002). The relationship between carotid IMT and CV events is a continuous one and determining a threshold for high CV risk is rather arbitrary. A carotid IMT >0.9 mm has been taken as a conservative estimate of existing abnormalities (European Guidelines 2012). A recent systematic review concluded that the added predictive value of carotid screening may be primarily found in asymptomatic individuals at intermediate CV risk, above and beyond traditional risk factors (Peters SA et al. 2012). In the IMPROVE trial a 12.1% reclassification improvement of patients at increased CV risk was found when information derived from a single cIMT was combined with classical risk factors (Baldassarre D et al. 2012). In the ARIC study (Nambi V et al. 2010) the IMT measurement and identification of plaque presence or absence improved CHD risk prediction and the conclusion was that it should be considered in the intermediate risk group. Adding cIMT and plaque information resulted in the reclassification of ~23% of the subjects, with a net reclassification improvement of ~9.9%. In the European guidelines (2012) vascular ultrasound screening is considered reasonable in risk assessment among asymptomatic individuals at moderate risk. In the European Lacidipine Study on Atherosclerosis (ELSA) baseline cIMT values but not treatment-induced changes in cIMT predict incident cardiovascular events in treated hypertensive patients (Zanchetti A et al. 2009). In the new 2013 ACC/AHA Cardiovascular Risk Guidelines (Andrus B and Lacaille D 2014) the cIMT is not recommended as a routine measurement in clinical practice for risk assessment of a first atherosclerotic cardiovascular (ASCVD) event because the addition of common cIMT measurements to the Framingham Risk Score (FRS) was associated with only small improvement in 10-year risk prediction of first-time myocardial infarction or stroke. This improvement is unlikely to be of clinical

importance (2013 ACC/AHA Guidelines, Den Ruijter HM et al. 2012). Standardization of cIMT measurement is also a major challenge (Den Ruijter HM et al. 2012).

3.5 Pulse wave velocity

Carotid-femoral pulse wave velocity (PWV) is the ‘gold standard’ for measuring aortic stiffness (Laurent S et al. 2006). Aortic stiffness has independent predictive value for fatal and non-fatal CV events in hypertensive patients (Vlachopoulos C et al. 2010). The additive value of PWV above and beyond traditional risk factors, including SCORE and Framingham risk score, has been quantified in a number of studies (Sehestedt T et al. 2010, Segestedt T et al. 2012, Boutouyrie P et al. 2002, Mattace-Raso FU et al. 2006). A substantial proportion of patients at intermediate risk could be reclassified into a higher or lower CV risk, when arterial stiffness is measured (Sehestedt T et al. 2010, Mattace-Raso FU et al. 2006, Mitchell GF et al. 2010).

According to the European Guidelines on cardiovascular disease prevention the measurement of carotid–femoral pulse wave velocity provides a comprehensive non-invasive assessment of arterial stiffness (damage in the arterial wall) and has an independent predictive value for all-cause and cardiovascular morbidity, coronary events, and strokes in patients with uncomplicated essential hypertension as well as in the general population (Perk J et al. 2012). However, the electronic, interactive version of SCORE—HeartScore is currently being adapted to allow adjustment for the impact of HDL cholesterol on total risk but not the PWV. The new 2013 ACC/AHA Cardiovascular Risk Guidelines do not recommend the PWV as an additive risk factor in the traditional risk scores.

Interestingly, systolic or pulse pressure seems to be a poor surrogate for stiffness in the young (McEniery CM et al. 2005, Ben-Shlomo Y et al. 2014) whereas the PWV is a stronger risk factor amongst younger individuals although it was weaker, but still predictive, in older individuals (Ben-Shlomo Y et al. 2014). Individuals with stiff aorta, who are susceptible to cardiovascular disease, die younger. Systolic hypertension in younger individuals seems to be driven predominantly by an elevated cardiac output and stroke volume and not by pulse wave reflection, which is also seen in exercise. The incident waves are the principal components of excess pressure load induced with exercise and there seems to be only a minor role for wave reflection in exercise central BP (Schultz MG et al. 2013). At older age the PWV is less predictive due to attenuation of elevated systolic blood pressure (Ben-Shlomo Y et al. 2014, Staessen J et al. 1990).

3.6 Endothelial dysfunction

Endothelial dysfunction predicts outcome in patients with a variety of CVDs, although data on hypertension are still rather scant (Lerman A and Zeiher AM 2005, Versari D et al. 2009). There are studies, which show that brachial FMD independently predicts long-term adverse CV events in healthy subjects with no apparent heart disease in addition to those derived from traditional risk factor assessment (Framingham risk score) (Shechter M et al. 2014, Yeboah J et al. 2009). In a long-term follow-up of the FATE study (Anderson TJ et al. 2011), FMD was, however, not predictive of subsequent cardiovascular events and remained an insignificant predictor when added to the Framingham risks score. In the recent HUNT3 Fitness Study (Skaug EA et al. 2012) the endothelial dysfunction (FMD $\leq 0\%$) was observed 17% in adults with no self-reported cardiovascular disease. Interestingly, the most marked reduction in endothelial function was found in middle-age with gender difference, about a decade before the age of the largest increase in incidence of first cardiovascular events. Lower FMD in middle-aged men probably indicates a substantial prevalence of subclinical atherosclerosis, supported by significantly higher frequency of endothelial dysfunction in men 40–59, compared to women. The endothelial dysfunction may precede cardiovascular disease, and thus could be useful for identifying high-risk individuals. In the meta-analysis of Inaba (Inaba Y et al. 2010) the impairment of brachial FMD was significantly associated with future cardiovascular events. The techniques available for investigating endothelial responsiveness to various stimuli are, however, laborious, time consuming and often invasive.

3.7 Coronary artery calcium (CAC)

Increase in coronary calcium, as identified by high-resolution cardiac computed tomography, has also been prospectively validated as a predictor of CVD and is highly effective in re-stratifying asymptomatic adults into either a moderate or a high CVD risk group (Greenland P et al. 2010, Perrone-Filardi P et al. 2011). The MESA investigators showed that the addition of CAC to a prediction model based on the traditional Framingham risk score significantly improved the classification of risk and placed more individuals in the most extreme risk categories (Polonsky TS et al. 2010). According to the 2013 ACC/AHA Guidelines CAC is likely to be the most useful of the current approaches to improving risk assessment among individuals found to be at intermediate risk after formal risk assessment (2013 ACC/AHA Guidelines). Limited availability, radiation exposure and high cost of the necessary instrumentations present serious problems, however.

3.8 Microalbuminuria

The renal damage is characterized by a reduced renal function and/or elevated urinary excretion of albumin (Stevens LA et al. 2006). While an elevated serum creatinine concentration or a lower GFR point to diminished renal function, the finding of an increased rate of urinary albumin or protein excretion indicates the existence of established renal parenchymatous disease. In both diabetic and non-diabetic hypertensive patients, microalbuminuria has been shown to predict CV events. Both in the general population and in diabetic patients, the concomitance of an increased urinary protein excretion and a reduced estimated GFR indicates a greater risk of CV and renal events than either abnormality alone, making these risk factors independent and cumulative (de Leeuw PW et al. 2004, Wachtell K et al. 2003, Arnlow J et al. 2005, Ninomiya T et al. 2009, Matsushita K et al. 2010).

The European Guidelines on cardiovascular disease prevention considered that the patients with moderate to severe chronic kidney disease may have higher risk than indicated in the charts (SCORE) (Perk J et al. 2012). According to the 2013 ACC/AHA Guidelines, however, the contribution of chronic kidney disease or albuminuria to the risk assessment of a first ASCVD event is uncertain at present. The new 2013 ESH/ESC Guidelines for the management of arterial hypertension found that an impaired renal function in a hypertensive patient constitutes a very potent and frequent predictor of future CV events and death (2013 ESH/ESC Guidelines).

3.9 Retinopathy

Hypertensive retinopathy by fundoscopy has prognostic significance in hypertensive patients, especially grade III and grade IV retinopathy have a high predictive value for mortality (Breslin DJ et al. 1966). Grade I and grade II point to early stage of hypertensive retinopathy and the predictive value for CV mortality is more controversial (Sairenchi T et al. 2011). Examination of the retina is not recommended in mild-to-moderate hypertensive patients without diabetes, except in young patients (2013 ESH/ESC Guidelines).

3.10 Mild cognitive impairment (MCI)

Several studies report that large artery stiffness (Kearney-Schwartz A et al. 2009, Mitchell GF et al. 2011) or elevated midlife systolic BP (Joas E et al. 2012, Stewart R et al. 2009, Muller M et al. 2014) increase the risk for late-life cognitive impairment or dementia. It seems that the longitudinal effects of vascular risk factors were significantly correlated with change in cognitive performance and less in memory performance

(Debette S et al. 2011). The brain is perfused at high-volume flow with very low vascular resistance. Elevated aortic stiffness is associated with progressive impedance matching between aorta and carotids and the normal impedance mismatch is lost, which enables the transmission of excessive pressure and flow pulsatility into the carotid circulation where these abnormal physical forces trigger microvascular damage (Picano E et al. 2014). This leads at the end to microvascular ischaemia, quantifiable tissue damage and reduced cognitive performance and later dementia (Mitchell GF et al. 2011). Hypertensive asymptomatic brain damage is seen in MRI as white matter hyperintensities, lacunar infarctions, and microbleeds. High cost does not allow widespread use of MRI in the evaluation of hypertensives. MRI may be used in the clinical assessment of elderly hypertensive's with neural or cognitive disturbances

Interestingly, low cardiovascular and cognitive performance in early adulthood were associated with an increased risk of mild cognitive impairment (MCI) and dementia later in life, and the highest risks were observed in individuals with a combination of low cardiovascular fitness and low cognitive performance (Nyberg J et al. 2014). Also alcohol and other drug intoxication, previous stroke and depression are important risk factors for early-onset dementia (Nordstrom P et al. 2013).

It seems that favourable cognitive and social lifestyle with good fitness delay the onset of cognitive decline and dementia irrespective of the presence, amount, or type of brain pathology, which has been interpreted as evidence of cerebral reserve (Bennett DA et al. 2014). Aerobic exercise is associated with a reduced risk of cognitive impairment and dementia; it may slow dementing illness (Ahlskog JE et al. 2011).

3.11 Ankle-brachial Index (ABI)

A low ankle-brachial index (ABI) (i.e. ≤ 0.9) signals PAD and, in general, advanced atherosclerosis, has predictive value for CV events, and was associated with approximately twice the 10-year CV mortality and major coronary event rate, compared with the overall rate in each Framingham risk category (Feringa HH et al. 2006, Fowkes FG et al. 2008). Furthermore, even asymptomatic PAD, as detected by a low ABI, has prospectively been associated in men with an incidence of morbid and fatal CV events approaching 20% in 10 years (Fowkes FG et al. 2008, De Buyzere ML et al. 2008). According to the new 2013 ACC/AHA Cardiovascular Risk Guidelines the ABI was associated with total CHD risk and leads to significant reclassification, and the pattern of reclassification is different by sex. However, there is no evidence that screening for and treatment of PAD in asymptomatic patients leads to clinically important benefits. The ABI may improve risk assessment; however, no evidence was found as to whether measuring ABI leads to better patient outcomes (2013 ACC/AHA Guidelines). The low ABI is an additional vascular marker with predictive ability, but it seems to be more a diagnostic tool for peripheral arterial disease than a marker of subclinical organ damage. High ABI or

elevated ankle blood pressure has not been evaluated as indicators of subclinical organ damage in the literature.

3.12 Risk estimation

At the beginning a disease is easy to cure, but difficult to diagnose; as time passes, not having been treated or recognized at the outset, it becomes easy to diagnose, but difficult to cure.'

Niccolo Machiavelli, *Il Principe*, 1513

3.12.1 General

The accurate prediction of cardiovascular (CV) risk has been one of the ultimate tasks of contemporary preventive CV medicine. A good biomarker has many requirements. It must differ between subjects with and without outcomes. It must predict future outcomes in prospective studies and add information to established risk markers (Vlachopoulos C 2012). Furthermore, a good biomarker changes predicted risk to a sufficient extent which is seen as an improvement in a randomized study. An assessment of potential biomarkers includes analysis of calibration, discrimination and reclassification. Calibration refers to the ability of individual biomarker(s) to correctly predict the proportion of individuals who will experience disease events. Among patients predicted to be at higher risk, there will be a higher number of events, whereas among patients identified as being at lower risk, there will be fewer events. Discrimination refers to the ability of biomarker(s) to distinguish between which of two individual patients is at a higher risk of an event. Reclassification refers to the ability to reclassify individuals into other risk categories based on models that include the new risk marker. This new net reclassification improvement (NRI) has been introduced to provide a quantitative estimate of correct minus wrong reclassifications, where correct reclassifications are associated with higher predicted risks for cases and lower predicted risks for noncases.

3.12.2 Risk estimation

Several computerized methods have been developed for estimating total CV risk (Pyörälä K et al. 1994, D'Agostino RB Sr et al. 2008, Conroy RM et al. 2003, Hippisley-Cox J et al. 2008, Ridker PM et al. 2008, Ridker PM et al. 2007, Woodward M et al. 2007, Vartiainen E et al. 2007), the Framingham Risk Score and European Systematic Coronary Risk Evaluation (SCORE) being among the most widely used. Recently new

Pooled Cohort Risk Equations were proposed by AHA/ACC expert working group, which reflect the USA population better. The outcome (endpoint) is also more exactly defined: fatal or nonfatal myocardial infarction, and fatal or nonfatal stroke (Goff DC et al. 2014). Their strengths and limitations of risk scoring have been reviewed recently (Cooney MT et al. 2009). The risk equations perform reasonably well, yet there remains considerable overlap in estimated risk between those who are affected by a cardiovascular event and those who are not (Berry JD et al. 2012, Schlendorf KH et al. 2009).

The European guidelines either use the SCORE model directly or a national modification of the SCORE model to assist clinicians in preventive decisions. The models typically predict the 10-year risk of a fatal CVD on the basis of gender, age (40–65 years), smoking habits, level of total cholesterol, and systolic blood pressure (SBP) without previous CVD events. Multivariable statistical models then measure the extent to which underlying average risk in the population is modified by standard demographic factors and established risk markers. The SCORE has been developed based on large European cohort studies (Conroy RM et al. 2003). It allows calibration of the charts for individual countries, which has been done for numerous European countries. The electronic, interactive version of SCORE, known as the Heart-Score, is adapted to also allow adjustment for the impact of high-density lipoprotein cholesterol on total CV risk (Perk J et al. 2012, Mancia G et al. 2013).

In the FINRISK calculator the coronary risk and stroke risk are calculated separately and cardiovascular risk is evaluated by adding the coronary risk and stroke risk together. In addition, HDL-cholesterol and diabetes are also included in the model (Vartiainen E et al. 2007).

Predicting a future CV event in individuals who have no prior history of cardiovascular disease has proven difficult when based solely on traditional risk factors and scoring systems (Allan GM et al. 2013, Støvring H et al. 2013). In a recent systematic review of 27 studies using the Framingham risk equation, the predicted-to-observed ratios ranged from an underprediction of 0.43 in a high-risk population to an overprediction of 2.87 in a low-risk population (Brindle P et al. 2006). A particular problem relates to young people with high levels of risk factors: a low absolute risk may conceal a high relative risk requiring advice for intensive lifestyle measures. Another problem relates to old people. In some age categories the majority, especially of men, will have estimated cardiovascular death risks exceeding the 5–10% SCORE level, based on age (and gender) only, even when other cardiovascular risk factor levels are relatively low (Cavanaugh-Hussey MW et al. 2008, Marma AK et al. 2009).

Many alternative approaches have been proposed, such as the lifetime CV risk estimation (Berry JD et al. 2012) or the New Zealand Heart Forecast use a ‘cardiovascular age’ metric (age gap) that was directly linked to the assessment of 5 year CVD risk. This scoring system also enables long term risk elevation because the competing risk is considered in the equation (i.e. cancer among smokers) (Wells S et al. 2010). Long-term

or lifetime risk information may be more appropriate to motivate therapeutic lifestyle change in younger individuals. Also the relative risk should be considered in young people (Perk J et al. 2012).

The incorporation of other novel risk markers has had partial success in improving prediction. In the new American guidelines the additional risk markers (diastolic BP, family history of ASCVD, moderate or severe chronic kidney disease and body mass index (continuous or categorical) did not, however, significantly improve discrimination for 10-year hard ASCVD risk prediction when added to the final base models. Other risk markers (hs-CRP, ApoB, microalbuminuria, cardiorespiratory fitness, CAC score, cIMT, and ABI) were considered as potential adjuncts to quantitative risk estimation (Goff DC et al. 2014). In European scoring system the PWV in hypertensive persons, cIMT, ABI and exercise electrocardiography may be considered for cardiovascular risk assessment in moderate risk asymptomatic adults.

3.12.3 Criticism

In daily practice the awareness of tools to calculate global CHD risk is extremely high. However, the majority of practicing physicians do not use CHD risk assessments (Goff DC et al. 2014, Cooney MT et al. 2009, Berry JD et al. 2012, Schlendorf KH et al. 2012, Perk J et al. 2012, Mancia G et al. 2013, Allan GM et al. 2013, Støvring H et al. 2006, Brindle P et al. 2006, Cavanaugh-Hussey MW et al. 2008, Marma AK et al. 2009, Wells S et al. 2010, Shillinglaw B et al. 2012). It is too time consuming, requires multiple measurements and the output of risk calculations with probabilities are difficult to understand by both clinicians and patients. Absolute risk-based recommendations are still not well understood by many practitioners or patients, and it is a significant barrier to the implementation of absolute CVD risk-based management. The traditional approach to CVD risk prediction and risk communication simply involves measuring blood pressure or blood lipids, then informing patients that their levels are too high and required treatment.

Interestingly, traditional risk factors such as elevated BP, hyperglycemia and raised cholesterol, which fluctuate over time with the follow-up of individual patients, may give only a snapshot at the time of measurement and not the whole history of arterial ageing and it seems that the age itself in equation integrates the long term effect of the established, as well as of the currently unknown risk factors on the arterial tree, together with the genetic individual predisposition.

At every level of risk factor exposure, there is substantial variation in the amount of atherosclerosis. This variation in disease is probably due to genetic susceptibility, combinations of different risk factors, and interactions between genetic and environmental factors. Thus evaluation of subclinical organ damage is useful for improving CVD risk prediction. The easiest measurement might be the PWV, which gives us valuable

information about arterial stiffness and reflects true arterial wall damage (Ben-Shlomo Y et al. 2014). It integrates and reflects the long-term effect of the established, as well as of the currently unknown risk factors on the arterial wall, together with the genetic predisposition of the individual. Elevated ankle blood pressure, on the other hand, might be a reflection of arterial stiffness.

4 AIMS OF THE STUDY

Long-term prospective and prognostic studies on the value of ankle blood pressure in middle-age persons are sparse. The present investigations had the following aims:

To investigate the value of ankle blood pressure, together with the brachial exercise blood pressure, as a predictor of cardiovascular and total mortality.

To assess prospectively the association of ankle blood pressure, together with the resting and exercise blood pressure, with coronary morbidity and mortality.

To investigate the utility of ankle blood pressure and pulse pressure as predictors of cerebrovascular events in a prospective setting.

To evaluate the association between the ankle blood pressure and clinically incident dementia in a large prospective follow-up study.

5 MATERIALS AND METHODS

5.1 Study population

Subjects for this investigation were derived from a group of 4,038 consecutive ambulatory patients, who underwent symptom-limited bicycle exercise test at the Helsinki Deaconess Institute between August 1989 and December 1995. The patients were referred by occupational health physicians to a symptom-limited exercise test to rule out coronary heart disease and evaluate physical fitness. More precisely, 1,734 were sent for the evaluation of physical fitness, 1,799 for diagnostic testing due to chest pain or shortness of breath, 488 because of suspected arrhythmias and 17 for mixed reasons, mainly for suspicion of exercise-induced asthma. Patients with a documented history of myocardial infarction, percutaneous coronary angioplasty, coronary artery bypass grafting, congestive heart failure or stroke, were excluded from the analysis. The final study group consisted of 3,858 patients. Of them, 759 persons were under medication and the antihypertension medication was the most important drug therapy (412 used b-blockers, 48 diuretics and 185 used angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers). In total, 52 persons had medication for diabetes.

Other risk factors assessed at baseline were age, gender, body mass index (BMI), smoking status, medical history, parental history of early cardiovascular disease, self-reported history of cardiovascular diseases, self-reported total cholesterol and glucose.

5.2 Baseline vascular examination

A 12-lead ECG was recorded before the exercise. Brachial blood pressure was measured by trained technicians using the auscultatory method with a standard sphygmomanometer from the left arm of the subject in a supine position after a 5 minute rest. The ankle blood pressure was simultaneously measured from the right leg using a Doppler probe with a mercury sphygmomanometer. The posterior tibial artery was used, and if absent, the ankle blood pressure measurements were taken from the dorsalis pedis artery.

5.3 Exercise test

Exercise ECG testing was conducted on an electronically braked bicycle. The starting load was 50 Watts for men and 40 Watts for women, and the load was increased every 3 minutes by 50 Watts for men and 40 Watts for women. Blood pressure was measured with a sphygmomanometer at 2 minutes at all loads and immediately prior to test termination. Readings were recorded to the nearest 5 mmHg. The 2-minute blood pressure recording at the moderate exercise level (150 W for men and 80 W for women) was used in the analyses. If that level was not reached, blood pressure from the lower level was used. The test was continued until a subject refused to continue, or until the attending physician felt it unsafe to continue. The criteria for myocardial ischaemia during the exercise test were ischaemic changes in ECG defined as ST depression >1.0 mm at 60 ms after the J-point with typical ischaemic complaints (chest pain or shortness of breath). The maximal power output is measured in watts and mathematically translated in METS.

5.4 Blood pressure groups

Subjects were divided into five groups based on resting ankle and exercise blood pressure at the moderate exercise level (men 150 Watt, women 80 Watt): 1) Reference group, where the resting ankle blood pressure was < 175 mmHg and the exercise blood pressure ≤ 215 mmHg; 2) patients with elevated ankle blood pressure (≥ 175 mmHg) but normal exercise blood pressure (≤ 215 mmHg); 3) patients with elevated ankle (≥ 175 mmHg) and elevated exercise blood pressure (>215 mmHg); 4) elevated exercise blood pressure (>215 mmHg), but ankle blood pressure <175 mmHg; and 5) patients who could not be classified.

Group 4 consists of patients with a discrepancy between the ankle blood pressure and brachial exercise systolic blood pressure, which indicated significant stenotic changes along the conduit vessels. The unclassifiable group could not reach the moderate exercise level because of a specified reason (for example ischaemic heart disease) or an unspecific reason (for example poor physical fitness).

Groups were constructed because they made sense pathophysiologically and because the ankle blood pressure has a U-shaped association with the risk of a coronary event and cannot therefore be analysed as a continuous variable. As there are no established reference values for the ABP or the brachial exercise blood pressure, we chose our cut-points (175 and 215 mmHg) arbitrarily to create groups of reasonable size. The group 5 was included in the analyses for the sake of completeness and also to examine the risk associated with poor physical fitness.

In dementia analyses, the groups were collapsed into four to ascertain a reasonable number of incident dementia cases for each group. The reference group included 'normal' patients with normal ankle-BP (<175 mmHg) and normal systolic blood pressure

(≤ 215 mmHg) at the moderate exercise level. Group 2 included patients with elevated ankle-BP (≥ 175 mmHg) but normal exercise blood pressure (≤ 215 mmHg). Group 3 had elevated exercise blood pressure with normal or elevated ankle-BP. Patients in group 4 were unclassifiable because they could not tolerate the moderate exercise level.

5.5 Follow-up procedures

For the original publication I the all cause mortality follow-up data were available up to 15 years (range 12–15 years) until December 31st, 2004. The coronary death or first non-fatal coronary event, including MI, percutaneous coronary angioplasty or coronary artery bypass graft surgery data were available up to 15 years (range 12–15 years) until 31 December 2006.

In the Causes-of-Death Register deaths were coded according to the Ninth (until Dec. 31st, 1995) and Tenth (since the beginning of 1996) versions of the International Classification of Diseases (ICD). The primary endpoint was cardiovascular death, and all-cause mortality was used as a secondary endpoint. ICD-9 codes 410 to 414, 431, 436, 798, 4330A, 4331A, 3339A, 4341A, 4349A, 4376A or ICD-10 codes I20–I25, I46, I61, I63–I64, R96, R98 as the underlying cause of death were taken as cardiovascular deaths. Altogether, 346 persons died during the follow-up, 108 of the deaths were cardiovascular. As a whole, the study consisted of 52,234 person-years of follow-up.

The follow-up for cerebrovascular event was 16 years, until the end of 2007. The endpoint was a major CV event, that is, death due to CV, nonfatal stroke, or a transient ischemic attack (TIA). We took as CV events the ICD-9 codes 431, 436, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, and 435 or the ICD-10 codes I61, I63–I64 and G45. Altogether, 170 CV events were observed during the follow-up. Of them, 31 were fatal. As a whole, the study consisted of 53,044 person-years of follow-up.

Deaths were ascertained by record linkage of the study data to the National Causes-of-Death Register, on the basis of the personal identification code unique to every resident of Finland. Non-fatal MIs, revascularizations and stroke or TIAs were identified from the national Hospital Discharge Register.

The coverage of follow-up was 100% for symptomatic events leading to hospitalization or death in Finland. It is however likely that all TIAs have not been hospitalized and those treated on an ambulatory basis are not identified as CV events in the present study. For this summary, the analyses were updated so that the follow-up time was 18 years, until the end of 2008.

The follow-up for incident dementia was 18 years, until the end of 2008. ICD-9 codes 2900A, 3320A, 3321A and ICD-10 codes F001–F009 and F01–F03 were used for the diagnosis of dementia. In 46 cases, the diagnosis was made on the basis of chronic use of dementia medication. These were identified using the Anatomic Therapeutic Classification codes N06DA02–N06DA04 and N06DX01 from the National Drug

Reimbursement Register containing all drugs prescribed by a doctor. The primary outcome was clinically incident dementia without subtyping.

5.6 Statistical methods

Data are expressed as mean \pm SD for continuous variables, or counts and proportions for categorical variables. The following cardiovascular risk factors were dichotomized: early parental cardiovascular death (under 60 years, yes or no), self-reported elevated cholesterol (>6 mmol/l, yes or no), self-reported elevated blood glucose (>6 mmol/l, yes or no) and current smoking (yes or no). Age, BMI, smoking (years, packet/day) and blood pressure (mmHg) were handled as continuous variables.

Continuous variables were compared between the blood pressure groups with analysis of variance and proportions with chi-square tests. Student's t-tests or Mann-Whitney U-tests were used for comparisons of normally distributed and skewed continuous variables.

Univariate associations between different blood pressure indicators were evaluated with Pearson's product-moment correlation coefficients. Associations between the blood pressure groups and mortality and morbidity (first event) were analyzed using Kaplan-Meier survival curves and log-rank tests. Cox proportional hazard models were used for estimating the multivariate-adjusted independent associations of the blood pressure groups with mortality and morbidity (first event). The proportional hazards assumption was examined graphically and was found to be valid. A gender-specific analysis was also performed to evaluate gender differences.

We carried out a sensitivity analysis by excluding those dementia cases where the diagnosis was made only on the basis of medication use, but the results remained consistent with the original findings. Therefore, the results obtained using the entire material are reported.

Results were expressed as hazard ratios (HR) and 95% confidence intervals (CI) compared to the reference group. The basic models were adjusted for age and sex. The larger models were further adjusted for BMI, physical working capacity (metabolic equivalents = METs), self-reported blood glucose and cholesterol, current smoking and early parental history of cardiovascular disease.

Statistical analyses were carried out using R (Versions 2.3.1–2.12.1; The R Foundation for Statistical Computing, Vienna, Austria).

6 RESULTS

6.1 Ankle blood pressure as a predictor of total and cardiovascular mortality (Study I)

The mean age at baseline was 50.5 ± 10.0 years (range 15–84), and the mean BMI was 26.1 ± 3.8 kg/m². The mean brachial blood pressure was $133.1 \pm 18.7/85.3 \pm 10.9$ mmHg and pulse 73.8 ± 12.9 /min. The correlation coefficient between the brachial blood pressure at rest and the ankle blood pressure was significant, 0.603 ($P < 0.0001$), but only 36% of variance of ankle blood pressure is explained by the brachial systolic PB (multiple $R^2 = 0.363$). The correlation coefficient between the brachial blood pressure at rest and the exercise blood pressure at the moderate exercise level (men 150 Watts, women 80 Watts) was 0.548 ($n = 2,313$, $P < 0.0001$) in men and 0.649 ($n = 1,211$, $P < 0.0001$) in women. The correlation coefficient between the ankle blood pressure and systolic blood pressure at the moderate exercise level was 0.543 ($P < 0.0001$) in men and 0.597 ($P < 0.0001$) in women. The resting brachial or ankle blood pressure explained only 29–30% (multiple $R^2 = 0.299$ and 0.287, respectively, of the exercise blood pressure) in men and 36–42% (multiple $R^2 = 0.420$ and 0.361, respective) in women. Due to the U-shaped association of the ankle blood pressure with brachial blood pressure and vascular events the study population is divided to different blood pressure categories at baseline.

The total mortality during follow-up (18 years) was 435 patients (11.3%), 145 (3.8%) due to cardiovascular causes and 207 (5.4%) due to cerebrovascular causes.

Table 1 compares cardiovascular risk factors in different blood pressure categories at baseline. The ABI differed significantly between the groups being highest in groups 2 and 3 and lowest in groups 4 and 5. The reference group ($n = 2,203$) was younger and leaner and all risk factors were more favourable compared with the other groups. In this group myocardial ischaemia during exercise was diagnosed in 94 patients. The total mortality was 125 patients (5.7%) and the mortality due to cardiac causes was 21 (0.95%) and 78 (3.5%) due to cerebrovascular causes.

In patients ($n = 791$) with elevated ankle blood pressure (≥ 175 mmHg) and normal exercise blood pressure the resting brachial blood pressure was normal or slightly elevated: $144 \pm 17/90 \pm 10$ mmHg. Of this group 36% were on cardiovascular medication. In patients without any medication ($n = 510$) the blood pressure was normal or slightly

elevated: $142.2 \pm 15/90.0 \pm 10.1$ mmHg. The total mortality was 146 patients (18.5%) and the mortality due to cardiac disease was 48 patients (6.1%) and 58 (7.3%) due to cerebrovascular causes.

Among patients ($n = 509$) with elevated ankle blood pressure and elevated exercise blood pressure male sex dominated. The brachial blood pressure at rest was elevated: $152.8 \pm 17/94.0 \pm 10$ mmHg. Compared with the previous group, BMI and ankle blood pressure were also higher and the smoking history was longer. In patients without any medication ($n = 348$) the mean blood pressure at rest was elevated: $150.6 \pm 16/93.1 \pm 10$ mmHg. Myocardial ischaemia during exercise was diagnosed in 44 (8.6%) patients. The total mortality was 71 patients (13.9%) and the mortality due to cardiac disease was 26 patients (5.1%) and 39 (7.7%) were due to cerebrovascular causes.

In patients with discrepancy between the ankle blood pressure and systolic blood pressure (group 4, $n = 222$) there was no correlation between the ankle blood pressure and exercise blood pressure at moderate level ($r = 0.050$, $p = 0.49$ among men and $r = 0.059$, $p = 0.80$ among women). Compared with the reference group the ankle blood pressure was a bit higher. The male sex dominated (201/21) and smoking was more common than in groups 1 and 2. Fifteen per cent were on cardiovascular medication. Myocardial ischaemia was diagnosed in 14 patients (6.3%). The total mortality was 31 patients (14.0%) and the mortality due to cardiac disease was 14 patients (6.3%) and 14 (6.3%) were due to cerebrovascular causes.

The fifth group ($n = 133$) was older. They could not tolerate moderate exercise level because of ischaemic heart disease ($n = 71$), leg atherosclerotic disease (ABI <0.97 , $n = 38$), abnormal lung function (oxygen saturation $<90\%$, $n=10$) or 43 without any specific reasons (low fitness). They tended to be current ($n = 19$) or ex-smokers ($n = 7$). The male sex dominated (103/30). Nine were on antihypertensive medication. The total mortality was 62 patients (46.6%) and the mortality due to cardiac disease was 36 patients (27.1%) and 18 (13.5%) were due to cerebrovascular causes.

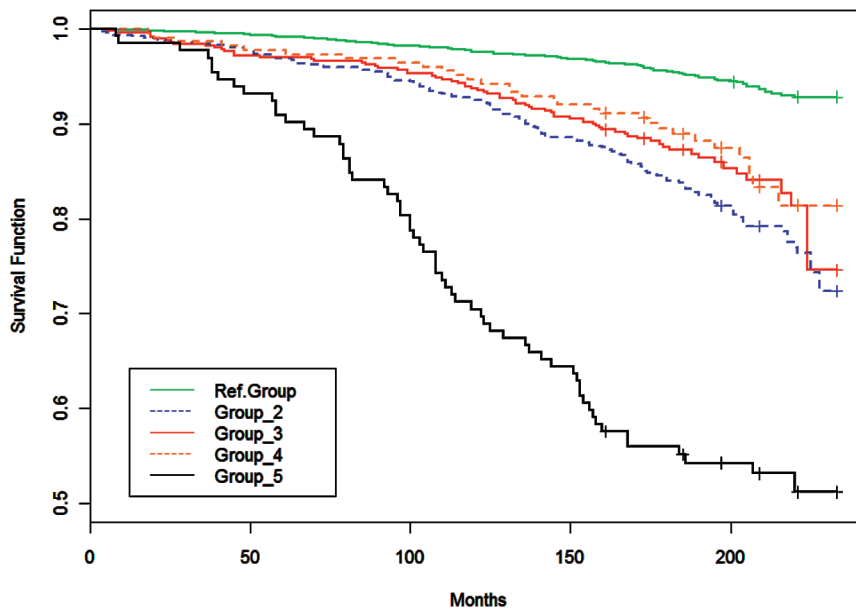
Figure 4 shows the Kaplan-Meier survival curves for total mortality in different blood pressure groups. The curves diverge continuously and significantly throughout the 18 years of follow-up. Compared with group 1, the age and sex-adjusted hazard ratios for total mortality were significantly elevated in all other groups (Table 2). Further adjustment for traditional risk factors, such as smoking, BMI and parental history of early CVD attenuated the HRs slightly, but they nevertheless remained clearly significant.

Table 1. Characteristics of the Study Participants by Ankle Blood Pressure (ABP) and Exercise Blood Pressure (EBP) Group.

	Reference Group n = 2203	Group 2 n = 791	Group 3 n = 509	Group 4 n = 222	Group 5 n = 133	p
Age (years)	47(10)	55(9)	54(7)	51(9)	59(10)	0.001*
Male/female	1409/794	439/352	427/82	201/21	103/30	0.001†
Body mass index (kg/m²)	25.4(4)	26.8(4)	27.5(4)	26.9(4)	25.7(4)	0.001*
Syst. BP (mmHg)	124(14)	144(17)	152(17)	135(16)	137(20)	0.001*
Diast. BP (mmHg)	82(9)	90(10)	94(10)	85(9)	85(11)	0.001*
Pulse/min	73(13)	75(13)	75(13)	74(13)	75(14)	0.001*
SBP80 (women)	172(20)	192(15)	229(11)	233(13)		0.001*
SBP150 (men)	186(18)	199(14)	236(16)	231(12)		0.001*
SBPMax	193	203	240	236	178.3	0.001*
Ankle blood pressure (mmHg)	150(17)	194(14)	198(18)	157(14)	141(37)	0.001*
ABI	1.21(0.38)	1.31(0.14)	1.27(0.17)	1.16(0.14)	1.03(0.27)	0.001*
ABI<0.97 (n, %)	66(3)	0 (0)	0 (0)	22 (1)	39 (29)	0.001†
Abnormal total cholesterol (n, %)	925(42)	340(43)	234(46)	122(55)	74(56)	0.001†
Abnormal glucose (n, %)	132(6)	95(12)	66(13)	27(12)	35(26)	0.001†
Pos.family history (n, %)	793(36)	324(41)	188(37)	95(43)	69(52)	0.005†
Pack-years of smoking	9(11)	9(12)	13(14)	14(13)	20(16)	0.001*
Curren smokers (n, %)	308(14)	71(9)	71(14)	36(16)	51(38)	0.001†
METs	8.4(3)	6.6(2)	7.4(2)	7.9(1.9)	4.6(1.5)	0.001*
Cardiovascular medication (n, %)	22(1)	285(36)	178(35)	22(15)	60(45)	0.001†
Diagnosed IHD (n, %)	88(4)	142(18)	46(9)	13(6)	72(54)	0.001†
Deaths during follow-up (n, %)	88(4)	119(15)	56(11)	22(10)	60(45)	0.001†
Cardiovasc.deaths (n, %)	20(0.9)	40(5)	20(4)	9(4)	23(17)	0.001†

Mean values (S.D.) or proportions (%), * ANOVA, † χ^2 test. SBP80 = systolic blood pressure at the exercise level of 80 Watts, SBP150 = systolic blood pressure at the exercise level of 150 Watts
 SBPMax = maximum systolic blood pressure during exercise
 ABI = Ankle Brachial Index, METs = Exercise capacity measured in metabolic equivalents

Kaplan-Meier Curves for Total Mortality



	2200	2175	2143	981
Ref.Group, n=2213	2200	2175	2143	981
Group 2, n=778	760	735	689	263
Group 3, n=510	496	486	462	134
Group 4, n=226	221	218	208	84
Group 5, n=132	123	104	85	50

Log-rank test for the survival difference between the blood pressure groups: $p < 0.0001$. The numbers indicate people remaining in the follow-up at different points of time. All participants were not followed up for 200 months. The reference group consists of persons with normal brachial pressure ($<140\text{mmHg}$), $\text{ABP} <175\text{mmHg}$ and exercise blood pressure $\leq 215\text{mmHg}$ at the moderate exercise level. Group 2 had elevated $\text{ABP} (\geq 175\text{mmHg})$ but normal exercise blood pressure. Group 3 had elevated ankle and exercise blood pressure. Group 4 had $\text{ABP} <175\text{mmHg}$ but elevated exercise blood pressure (discrepancy) and group 5 could not be classified because of poor exercise tolerance.

Figure 4. Kaplan-Meier survival curves for total mortality.

Table 2. Hazard Ratios (HR, 95% Confidence Interval (CI)) of Total Mortality According to Specified Blood Pressure Groups.

Total Mortality (n=3859, total mortality = 435)						
	Model 1			Model 2		
	RR	95% CI	P-values	RR	95% CI	P-values
Group I	1	(reference)		1	(reference)	
Group II	2.26	1.77–2.90	<0.0001	1.72	1.30–2.28	<0.0001
Group III	1.78	1.32–2.39	<0.0001	1.27	0.90–1.80	0.173
Group IV	1.92	1.29–2.85	0.001	1.58	1.05–2.36	0.03
Group V	4.51	3.25–6.26	<0.0001	2.39	1.64–3.46	<0.0001

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, BMI, smoking, early parental cardiovascular disease and physical working capacity (METs)

6.2 Ankle and exercise blood pressures as predictors of coronary morbidity and mortality (Study II)

A total of 436 coronary events occurred during the follow-up of 18 years. There were 145 deaths due to CHD, 122 non-fatal MIs, 77 percutaneous coronary angioplasties and 147 persons with coronary artery bypass grafting. Differences in baseline characteristics between persons with and without a CHD event during the follow-up are presented in Table 3. Persons with a CHD event were older, especially women (62 years). In persons without a CHD event, almost all risk factors were more favourable compared with the CHD event group.

Table 4 compares cardiovascular risk factors in different blood pressure groups. The reference group was younger and all risk factors were more favourable compared with the other groups. In the reference group, 4% of individuals had positive exercise test without a CHD event in the follow-up.

Figure 5 shows the Kaplan-Meier curves of the five blood pressure groups for all CHD events. The curves clearly show the best prognosis of the group with normal ankle and exercise brachial blood pressures and the worst prognosis of the group with poor physical performance (group 5). The curves of the other groups (groups 2–4) are very close to each other between the two extremes.

The most significant predictors of CHD event were age (HR 1.06, 95% CI 1.04–1.07, $P < 0.0001$), gender (HR, women compared with men, 0.27, 95% CI 0.21–0.36, $P < 0.0001$), SBP (HR 1.01, 95% CI 1.01–1.02, $P < 0.0001$), physical performance (METs, HR 0.79, 95% CI 0.75–0.84, $P < 0.0001$), positive family history (HR 1.45, 95% CI 1.19–1.76, $P = 0.0002$) and pack-years of smoking (HR 1.01, 95% CI 1.01–1.02, $P = 0.0003$) when self-reported elevated cholesterol and self-reported elevated blood glucose were adjusted for.

The age- and sex-adjusted and the multivariate adjusted HRs of a CHD event in the different blood pressure groups are shown in Table 5. Compared with the reference group, the most elevated risk was seen in group with poor physical performance (group 5). The persons with elevated ABP without exaggerated exercise brachial blood pressure and normal or slightly elevated resting brachial blood pressure ($144 \pm 16/90 \pm 10$ mmHg) had 2.10-fold risk of a CHD event compared with the reference group.

Further adjustment for traditional risk factors, such as smoking, BMI, parental history of early CVD, self-reported elevated cholesterol and blood glucose attenuated the HR slightly, but it nevertheless remained clearly significant (1.68-fold). The persons with elevated ABP and exaggerated brachial exercise blood pressure at a moderate exercise level had a 2.09-fold risk in the basic model and 1.80-fold risk in the larger model compared with the reference group. In this group, the resting brachial BP was also elevated ($153 \pm 17/94 \pm 10$ mmHg). In persons with a discrepancy between the ankle and exercise brachial blood pressures, that is, normal ABP and elevated exercise brachial blood pressure (group 4), the risk of a future coronary event was even higher (2.63-fold

in the age and sex adjusted model and 2.29-fold in the multivariate adjusted model). The resting brachial blood pressure was normal or slightly elevated ($135 \pm 15/86 \pm 9$ mmHg).

In general, the HRs were higher for fatal than for non-fatal CHD events. The persons with poor physical performance (group 5) had the highest risk for fatal outcome (15.9-fold in the basic model and 7.02-fold in the larger model). In groups 2–4, the risk of CHD death was about 3.03- to 4.62-fold in the basic model and about 3.03- to 4.16-fold in the larger model. In addition, the risk of a non-fatal CHD event was significant for all groups in both models.

Also the HRs remains significant, when the brachial systolic blood pressure was added in the multivariate model (Group 2, HR 1.4, 95% CI 1.05–1.87, $P=0.02$; Group 3, HR 1.37 95% CI 1.00–1.90, $P=0.05$; Group 4 HR 2.1, CI 95% 1.47–3.0, $P<0.0001$; Group 5, HR 3.2, 95% CI 2.2–4.7, $P<0.0001$).

For comparison, we also calculated the HRs for the usual brachial systolic blood pressure, for exercise brachial blood pressure and for ABP alone. The resting brachial systolic blood pressure was dichotomized at 160mmHg (≤ 160 vs >160 mmHg). In the basic model, that is, adjusted for age and sex only, the HR for a CHD event was 1.83 (1.39–2.41, $P<0.0001$). In the larger model, the HR was 1.40 (1.05–1.85, $P=0.02$). The same comparison was repeated using the fatal CHD event as the outcome. In the basic model, the HR was 2.80 (1.87– 4.17, $P<0.0001$) and in the larger model the HR was 2.02 (1.33–3.06, $P=0.0009$). In persons with elevated exercise blood pressure (>215 mmHg) at the moderate exercise level, the HRs for fatal or nonfatal CHD event were also significant elevated (1.3–fold).

When analysing the ABP alone, we considered four mutually exclusive categories: (1) ABP <175 mmHg was taken as the ‘normal’ or reference category; (2) ABP between 175–215mmHg was taken as the ‘moderately elevated ABP’ category; (3) ABP >215 mmHg was taken as the ‘high ABP’ category; and (4) persons with abnormal ABI (<0.97) were considered as their own category. In persons with moderately elevated ABP, the HRs for fatal and non-fatal CHD event did not reach statistical significance in any of the models (data not shown). In persons with high ABP, the HR for a fatal and non-fatal CHD event was significantly elevated in both models, 2.11 (1.05–4.27, $P=0.04$) and 1.49 (1.12–1.98, $P=0.006$). Also, in persons with abnormal ABI, the HR for a fatal and non-fatal CHD event was significant in both models, 3.34 (1.34–8.31, $P=0.01$) and 1.91 (1.24–2.96, $P=0.004$).

Table 3. Baseline Characteristics of Participants With and Without Incident Coronary Heart Disease Event During the Follow-up.

	No CHD Event n=3423	CHD Event n=436	p
Age (years)	50 (10)	56 (9)	0.0001*
Men/women, n (%)	2217 (65) / 1206 (35)	344 (79) / 92 (21)	0.0001†
Body mass index (kg/m ²)	26.0 (4)	26.9 (4)	0.0001*
Syst. blood pressure (mmHg)	132 (18)	142 (19)	0.0001*
Diast. blood pressure (mmHg)	85 (11)	88 (10)	0.0001*
Pulse /min	74 (13)	73 (12)	NS
SBP80 (women)	181 (25)	198 (21)	0.0001**
SBP150 (men)	200 (26)	213(27)	0.0001**
SBPMax	203 (27)	207 (31)	0.005*
Ankle blood pressure (mmHg)	165 (26)	172 (32)	0.0001*
ABI	1.21 (0.22)	1.18 (0.2)	0.01*
Current smokers, n (%)	543 (15%)	103 (28%)	0.0001†
Self-reported abnormal total cholesterol, n (%)	1256 (36%)	198 (45%)	0.0001†
Self-reported abnormal blood glucose, n (%)	230 (7%)	60 (14%)	0.0001†
Pos. family history, n (%)	1256 (37%)	183 (42%)	0.009 †
METs	7.9 (3)	6.5 (2)	0.0001*
Blood pressure groups			
Group I (reference)	2085 (61%)	128 (29%)	
Group II	662 (19%)	116 (27%)	
Group III	425 (12%)	85 (19%)	
Group IV	181 (5%)	45 (10%)	
Group V	70 (3%)	62 (15%)	0.0001†

Data are mean (S.D.) or n and proportions (%), * t-Test,** Mann-Whitney U Test, † χ^2 test

SBP80=systolic blood pressure at the exercise level of 80 Watts

SBP150=systolic blood pressure at the exercise level of 150 Watts

SBPMax=maximum systolic blood pressure during exercise

ABI=ankle brachial index

METs=physical working capacity in metabolic equivalents

Please see the Methods-section for the explanation for the blood pressure groups.

Table 4. Baseline characteristics of participants by the ankle and exercise blood pressure group

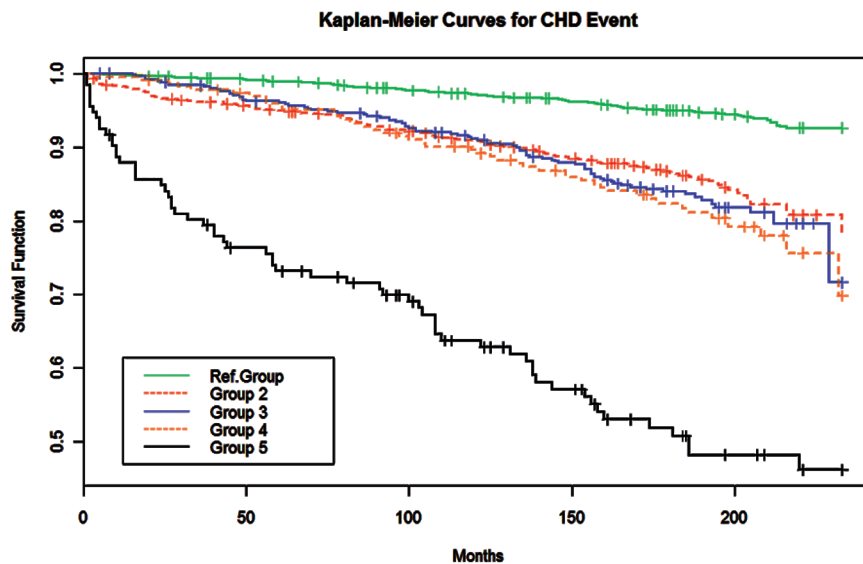
	Group 1 n=2213	Group 2 n=778	Group 3 n=510	Group 4 n=226	Group 5 132	P
Age	47(10)	55(9)	54(7)	51(9)	59(10)	0.0001a
Male/female	1379/800	428/344	417/80	206/20	101/34	0.0001b
BMI (kg/m ²)	25.4(4)	26.8(4)	27.5(4)	26.8(4)	25.6(4)	0.0001a
SBP (mmHg)	124(14)	144(17)	152(17)	135(16)	137(20)	0.0001a
DBP(mmHg)	81(9)	90(10)	94(10)	85(9)	84(11)	0.0001a
ABP(mmHg)	150(17)	194(14)	198(18)	157(14)	141(37)	0.0001a
Antihypertens. medication (n, %)	214(10)	241(31)	133(27)	27(12)	53(39)	0.0001b
Elevated cholesterol (n, %)	727(33)	338(43)	233(46)	106(47)	50(38)	0.0001b
DM(n,%)	91(4)	92(12)	65(13)	18(8)	24(18)	0.001b
Pack-years of smoking	9(11)	9(12)	13(14)	14(13)	20(16)	0.0001a

Please see the Materials and methods section for the explanation for blood pressure groups

Data are mean (s.d.) or n and proportions (%)

a Analysis of variance

b χ^2 -Test



Ref. Group, n=2179	2147	2094	1632	142
Group 2, n=772	720	680	467	38
Group 3, n=497	468	440	274	13
Group 4, n=226	216	200	145	14
Group 5, n=135	98	78	52	7

The numbers indicate people remaining in the follow-up at different points of time.

Figure 5. Kaplan-Meier Curves for CHD Event

Table 5. Hazard Ratios (HR, 95% Confidence Interval (CI)) of nonfatal, fatal and all CHD events according to specified blood pressure groups.

	Model 1			Model 2		
	RR	95% CI	P-values	RR	95% CI	P-values
Nonfatal CHD events,n=291						
Group 1	1	(reference)		1	(reference)	
Group 2	1.66	1.21–2.228	0.002	1.36	0.98–1.88	0.06
Group 3	1.90	1.36–2.64	0.0001	1.60	1.15–2.24	0.005
Group 4	2.3	1.53–3.45	<0.0001	1.90	1.32–2.90	0.001
Group 5	4.60	2.95–7.19	<0.0001	2.45	1.48–4.05	0.0005
Fatal CHD events,n=145						
Group 1	1	(reference)		1	(reference)	
Group 2	4.29	2.54–7.25	<0.0001	3.30	1.93–5.76	<0.0001
Group 3	3.36	1.88–6.02	<0.0001	3.03	1.67–5.48	<0.0001
Group 4	4.62	2.34–9.14	<0.0001	4.16	2.08–8.33	<0.0001
Group 5	15.90	8.91–28.37	<0.0001	7.02	3.60–13.64	<0.0001
All CHD events,n=436						
Group 1	1	(reference)		1	(reference)	
Group 2	2.10	1.62–2.72	<0.0001	1.68	1.28–2.19	0.0001
Group 3	2.09	1.58–2.78	<0.0001	1.80	1.35–2.39	<0.0001
Group 4	2.63	1.86–3.71	<0.0001	2.29	1.62–3.23	<0.0001
Group 5	6.45	4.65–8.94	<0.0001	3.38	2.32–4.91	<0.0001

Model 1: adjusted for age and sex adjusted

Model 2: adjusted for age, sex, BMI, smoking, early parental cardiovascular disease and physical working capacity(METs), self-reported elevated cholesterol and abnormal blood glucose

6.3 Ankle blood pressure and pulse pressure as predictors of cerebrovascular morbidity and mortality (Study III)

A total of 170 subjects developed a cerebrovascular event (30 TIAs, 109 nonfatal strokes and 31 fatal strokes) during the follow-up. Baseline characteristics of the study participants are outlined in Table 6, stratified by the cerebrovascular event. The patients with a cerebrovascular event were older and the blood pressures were higher. In patients without a cerebrovascular event almost all other risk factors were more favorable compared with the cerebrovascular event group.

Figure 3 shows Kaplan-Meier curves for cerebrovascular event in different blood pressure groups. The curves diverge continuousl and significantly (P = .001, log rank test) throughout the 16 years of follow-up. The patients with elevated ankle blood pressure with or without exaggerated exercise blood pressure had 2.6–2.7-fold risk of a cerebrovascular event compared with the reference group in the age- and gender-adjusted model (Table 7). In the wider model the hazard ratio was 2.2–2.4. In patients with obstructive changes in leg arteries (Group 4) the risk of a future cerebrovascular

event was 2.7-fold in the basic model and 2.4-fold in the multivariate adjusted model. The greatest hazard ratio (7.8 in the basic model and 5.8 in the wider model) was found in the unclassifiable patients (Group 5). In this group, 55 patients had ABI <1.0, and 25 patients had ABI <0.9.

Pulse pressures in the five blood pressure groups were 42.7±11, 54.4±15, 58.5±14, 49.0±14, and 52.6±16mmHg, respectively. Correlation between the pulse pressure and the ankle blood pressure in the blood pressure groups I–III was high ($r^2 = 0.48$). The correlation was lost, however, when obstructive changes were observed in the conduit vessels (Group 4) ($r^2 = 0.11$). The risk of a cerebrovascular event by quartile of pulse pressure is shown in Table 8. The reference category is the lowest quartile of the pulse pressure. Significantly elevated risk for a cerebrovascular event was found only for the fourth quartile in the smaller model.

Table 6. Baseline Characteristics of Participants With and Without Incident Cerebrovascular Event During the Follow-up.

	No Cerebrovascular Event n=3639	Cerebrovascular Event n=170	p
Age (years)	50 (10)	57 (10)	0.0001*
Men/women,n (%)	2423 (67)/ 1216 (33)	105 (62)/ 65 (38)	NS
Body mass index (kg/m ²)	26.1 (4)	26.6 (4)	NS
Syst.blood pressure (mmHg)	133 (18)	142 (19)	0.0001 *
Diast.blood pressure (mmHg)	85 (11)	89 (10)	0.0001 *
Pulse / min	74 (13)	74 (12)	NS
SBP80 (women)	181 (25)	193 (23)	0.001*
SBP150 (men)	201 (27)	212 (30)	0.0001 *
SBP Max	203 (28)	205 (29)	NS
Ankle blood pressure (mmHg)	165 (27)	174 (34)	0.0001 *
ABI	1.21 (0.2)	1.20 (0.2)	NS
Current smokers, n (%)	769 (22)	45 (29)	0.05 †
Self-reported abnormal total cholesterol, n (%)	1352 (37)	77 (45%)	0.001 †
Self-reported abnormal glucose, n (%)	273 (8)	20 (12)	0.04†
Pos. family history, n (%)	1365 (38)	67 (39)	0.6
METs	7.8 (3)	6.4 (2)	0.0001*
Blood pressure groups			
Group I (reference)	2125 (58%)	44 (26%)	
Group II	719 (20%)	56 (33%)	
Group III	467 (13%)	30 (18%)	
Group IV	214 (6%)	14 (8%)	
Group V	114 (3%)	26 (15%)	0.0001†

Data are mean (S.D.) or n and proportion (%), * t-Test, † χ^2 test

SBP80=systolic blood pressure at the exercise level of 80 Watts

SBP150=systolic blood pressure at the exercise level of 150 Watts

SBPMax=maximum systolic blood pressure during exercise

ABI=ankle brachial index

METs=physical working capacity in metabolic equivalents

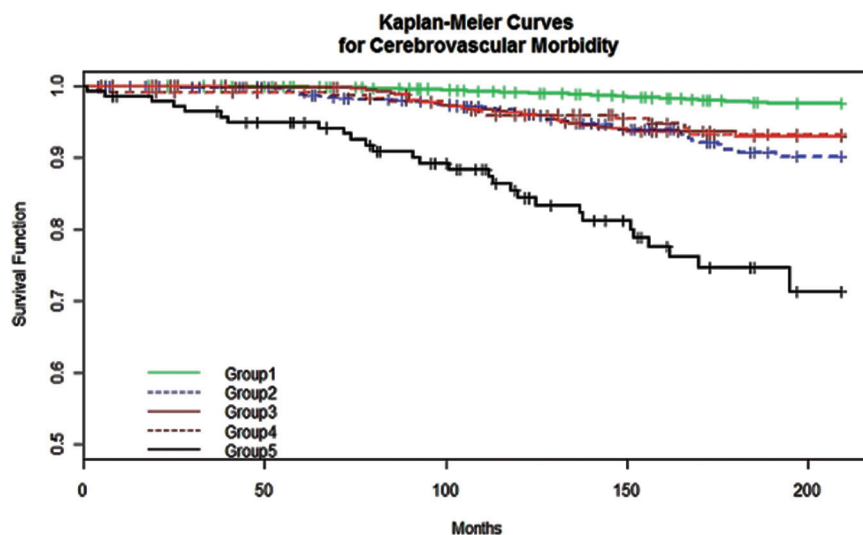
Please see the Materials and methods section for the explanation for blood pressure groups

Table 7. Hazard Ratios (HR, 95% Confidence Interval (CI)) of Cerebrovascular Events According to the Specified Blood Pressure Groups (Total n=3808, no of events=170).

Groups	Model 1			Model 2		
	HR	95 % (CI)	P-values	HR	95% CI	P-values
Group I	1	(reference)		1	(reference)	
Group II	2.69	1.78–4.07	<0.0001	2.24	1.43–3.52	<0.0001
Group III	2.60	1.60–4.20	<0.0001	2.09	1.21–3.61	0.008
Group IV	2.71	1.44–5.10	0.002	2.37	1.31–4.69	0.007
Group V	7.82	4.67–13.12	<0.0001	5.78	3.31–10.10	<0.0001

Model 1:adjusted for age and sex

Model 1:adjusted for age,sex,BMI,systolic RR,smoking,early parenteral vascular disease,METs, self-reported elevated cholesterol and blood glucose



Ref. Group 1, N=2169	2154	2123	1655	147
Group 2, N=775	757	721	492	39
Group 3, N=497	483	464	285	13
Group 4, N=228	221	214	157	13
Group 5, N=125	125	100	70	5

The numbers indicate people remaining in the follow-up at different points of time.

Figure 6. Kaplan-Meier Curves for Cerebrovascular Morbidity

Table 8. Hazard Ratios (HR, 95% Confidence Interval (CI)) of Cerebrovascular Events by Quartile of Pulse Pressure

	Model 1			Model 2		
	HR	95% CI	P-values	HR	95% CI	P-values
Quartile I	1	(reference)		1	(reference)	
Quartile II	0.91	0.54–1.53	0.7	0.92	0.55–1.56	0.7
Quartile III	1.28	0.80–2.07	0.3	1.21	0.75–1.95	0.4
Quartile IV	1.62	1.04–2.65	0.03	1.47	0.95–2.33	0.08

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, BMI, smoking, early parental cardiovascular disease and physical working capacity (METs), self-reported elevated cholesterol and abnormal blood glucose.

6.4 Ankle blood pressure and dementia: a prospective follow-up study (Study IV)

Over the 18-year follow-up (60 266 person-years), 123 of the 3859 (3%) patients developed clinically incident dementia, including 44 with a new cardiovascular or cerebrovascular event. Altogether, 592 patients had a vascular event (15%). The clinical characteristics of the study population are shown in Table 9, stratified by incident dementia. Patients with incident dementia were older than those without dementia and the majority of them were women. The resting brachial systolic and ankle-BP were higher in patients who developed dementia than in those who remained free of dementia, but there were not significant differences in diastolic blood pressure, BMI, or in self-reported cholesterol and blood glucose between the groups. The physical working capacity was better and pack-years of smoking were higher in patients who remained free of dementia than in the patients who developed dementia. The distribution of participants to the four blood pressure groups differed significantly by the status of dementia. Moreover, antihypertensive medication was more common in patients with future dementia.

Fifty-two patients with dementia (44.7% of the total 123) died during the follow-up, 15 because of a cardiac event and 14 because of a cerebrovascular event. Of the patients with dementia who survived, 14 had a cardiac event and six had stroke.

In the four blood pressure groups, dementia was observed in 43 (2%) patients in group 1, 49 (6%) in group 2, 14 (2%) in group 3, and 17 (13%) in group 4. However, a cardiovascular or cerebrovascular event was diagnosed in 195 (8.8%) patients in group 1, 158 (20.3%) in group 2, 172 (23.3%) in group 3, and 67 (50.7%) in group 4, respectively. In the unclassifiable group, there were 17 patients with incident dementia; nine of these died during the follow-up, seven because of vascular causes. Four out of the eight patients who survived had a nonfatal vascular event. Abnormal ankle brachial index (<0.9) at baseline was measured in eight patients. Almost half (47%) of this unclassifiable group died of cardiovascular or cerebrovascular causes during the follow-up period.

Figure 7 shows the Kaplan-Meier curves for clinically incident dementia in different groups. In groups 2 and 4, the curves diverged continuously and significantly ($P>0.001$, log-rank test) throughout the 18 years of follow-up. The patients with elevated ankle-BP without exaggerated exercise blood pressure had a 1.58-fold risk of dementia compared with the reference group in the age-adjusted and sex-adjusted model and the hazard ratio was 1.59 in the wider model (Table 10). The observed hazard ratios were independent of resting brachial systolic blood pressure and several other potential confounders. In group 3, the statistical analysis is uncertain because of the small number of patients with dementia (14 patients). For comparison, we calculated the hazard ratio for the brachial systolic blood pressure. We could not find any association between the systolic brachial blood pressure and dementia (Table 10). Only low cardiac fitness was associated with dementia ($P=0.01$). The results did not change considerably when the brachial systolic

blood pressure was replaced with pulse pressure. The hazard ratio for pulse pressure was 1.0 (95% CI 0.99–1.01) (P=0.89).

Table 9. Characteristics of participants who developed incident dementia during the follow-up and those who remained free of dementia.

	Dementia, n=123	No dementia, n=3736	P
Age,years	63.7(7.7)	49.9(9.6)	>0.0001
Men/women, n (%)	46/77 (63%)	2515/1221 (33%)	>0.0001†
SBP,mmHg	138(20)	135(20)	0.002
DBP,mmHG	85(9)	85(11)	0.7
Pulse/beats min	72(13)	74(13)	0.05
SBP80(women)	188(24)	182(25)	0.06
SBP150(men)	205(24)	201(27)	0.35
ABP, mmHg	173(31)	165(27)	0.01
ABI-index	1.21(0.4)	1.20(0.3)	0.72
Smoking(years)	7.5(12)	9.7(12.5)	0.04
BMI (kg/m ²)	26.1(3.9)	26.1(3.8)	0.92
Self-erported abdorm.total cholesterol, n(%)	48/75(39%)	1405/2329(38%)	0.83
Self-reported abnormal glucose, n(%)	12/111(10%)	278/3455(7%)	0.43
Antihypertensive medication,yes,no,(%)	46/77(37%)	623/3113(17%)	>0.0001†
Blood pressure groups			
Group 1 (reference)	43(35%)	2170(58%)	
Group 2	49(40%)	2170(58%)	
Group 3	14(11%)	722(19)	
Group 4	17(14%)	115(3%)	0.0001†

*Data are mean (SD) or N (%)

Please see the Materials and methods section for the explanation for blood pressure groups

Table 10. Hazard Ratios (HR, 95% Confidence Interval (CI) of Dementia According to the Specified Blood Pressure Groups (Total n=3859, no of dementia=123).

Blood Pressure Group	HR	95 % (CI)	P-value	HR	95 % (CI)	P-value
Group 1	1 (reference)			1(reference)		
Group 2	1.58	1.04–2.40	0.034	1.59	1.00–2.56	0.05
Group 3	0.82	0.44–1.52	0.53	0.9	0.45–1.77	0.74
Group 4	2.26	1.24–4.13	0.008	1.93	1.00–3.80	0.05

Model 1: adjusted for age and sex

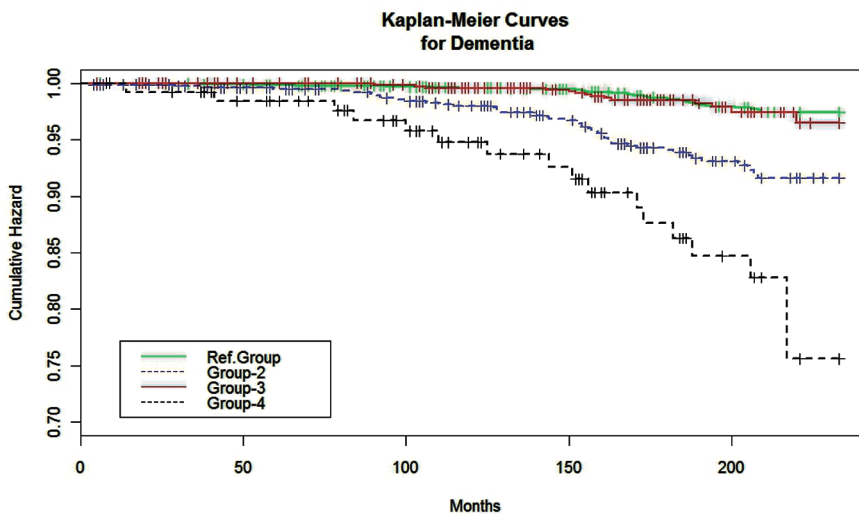
Model 2: adjusted for age, sex, smoking, physical working capacity (METs), early parental cardiovascular disease and resting brachial systolic blood pressure

Table 11. Cox proportional hazards ratios, dependent variable: dementia.

	β	Harzard ratio	95 % (CI)	P-value
Age(years)	0.15	1.16	1.13–1.19	<0.001
Gender	0.38	1.46	0.92–2.32	0.1
SBP,mmHg	-0.002	0.98	0.99–1.03	0.67
BMI (kg/m ²)	-0.017	0.98	0.93–1.03	0.51
METs	-0.179	0.84	0.73–0.96	0.01
Current smoking	-0.004	1.0	0.98–1.01	0.64
Pos.family history	0.197	1.22	0.83–1.78	0.31

METs: physical working capacity in metabolic equivalents.

Pos. family history: early parenteral cardiovascular disease



Ref.Group (n=2213)	2198	2169	2133	965
Group 2 (n=778)	757	725	673	253
Group 3 (n=736)	717	703	667	214
Group 4 (n=132)	122	103	83	45

Figure 7. Kaplan-Meier Curves for Dementia

7 DISCUSSION

7.1 Summary of the main findings

This study confirmed that the ankle blood pressure gives us important information about the status of the arterial tree in middle-aged asymptomatic individuals. The main finding was that even those persons among whom the elevated ankle blood pressure was the only abnormal finding had 1.7-fold higher multivariate-adjusted risk of death, especially cardiovascular or cerebrovascular death (3.3- vs. 2.2-fold). The elevated ankle blood pressure had an independent predictive value even for dementia (1.6-fold), probably due to its role as a marker of arterial stiffness or atherosclerosis. On the other hand, persons with normal ankle, arm and exercise brachial blood pressure had clearly the best prognosis. The total mortality was 5.7% and the mortality due to cardiac causes was only 0.95% (21 patients) and 3.5% (78 patients) due to cerebrovascular causes during the follow-up of 18 years. An abnormal increase in ankle blood pressure with or without exaggerated exercise BP reaction may act as a forewarning of increased CV risk to clinicians, irrespective of resting BP.

7.2 Participants and methods

We had a large cohort of over 4000 patients and a complete follow-up ranging from 15-18 years in different substudies. The numbers of incident cardiovascular outcome events were large but the number of incident dementia cases was a bit more limited. The ankle BP was measured using the Doppler method, which is considered as the golden standard (Aboyans A et al. 2012). The exercise electrocardiograms were performed following a standard protocol that is commonly used in clinical work in Finland. The main statistical analyses were carried out using Cox proportional hazards regression analyses after checking for the validity of the proportional hazards assumption. As always, the study has some limitations, which are discussed in more detail below in paragraph 7.6, but as a whole, we believe that the materials and methods used for the study, are well suitable for answering the questions posed in the beginning of the study and presented above in paragraph 4.

7.3 Ankle and exercise blood pressure

Like brachial blood pressure, the ankle blood pressure (ABP) is a biological variable and there is no cut-off point separating normal from abnormal pressure. According to the ESH/ESC guidelines, hypertension is defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg DBP, based on the evidence from the randomized controlled trials (RCTs) demonstrating that in patients with these BP values treatment-induced BP reductions are beneficial. One cut-off point that has been used is the level of arterial blood pressure associated with doubling of long-term cardiovascular risk (Mancia G et al. 2013). It seems that the relation of systolic blood pressure to mortality is U-shaped, with the lowest risk at a pressure of about 130 mmHg (Sundström J et al. 2011).

The main determinants of ABP are systolic blood pressure, enhanced pulse pressure, and local changes caused by rigidity of the arteries in the lower extremities, when the large conduit vessels are free of flow limiting atherosclerotic stenoses. In these conditions, we can draw epidemiologic conclusions from ABP per se without indexing it to the brachial systolic pressure. It is, however, difficult to assess, when the stenotic changes along the conduit vessels begin to decrease the ankle blood pressure. Mild stenotic peripheral artery disease may not be detected by decreased ABI at rest because severe stenosis in at least one major artery is needed to reduce the ankle pressure.

During normal exercise, cardiac output increases in response to the demand of working muscles because of a sympathetically mediated increase in heart rate and stroke volume. Arterial pressure, both peripheral and central, rises in a graded fashion with increasing exercise intensity. Systemic vasodilatation offsets the rise in cardiac contractility, heart rate, and left ventricular output, resulting in increased peripheral blood flow (Sharman JE et al. 2005). Increased cardiac output, decreased peripheral vascular resistance, and their interactions determine blood pressure during exercise. The exercise causes a systemic vasodilatation and backward wave augmentation is reduced (Munir S et al. 2008, Schultz MG et al. 2013, Schultz MG et al. 2013).

When cardiac output is not balanced by increased compliance from peripheral muscle vasculature dilation, the result is a sharp increase in systolic blood pressure. The mechanisms underlying an excessive increase in systolic blood pressure are likely multifactorial, such as a reduction in aortic compliance (stiffness) together with structural abnormalities in the peripheral vasculature, an inability of the peripheral vasculature to appropriately vasodilate in exercise or impaired endothelial function (Fagard RH et al. 1996, Dachun X et al. 2010, Suominen V et al. 2008, Aboyans V et al. 2008, Stewart KJ et al. 2004, Thanassoulis G et al. 2012, Sung J et al. 2012). According to Tsiachris (Tsiachris D et al. 2010) exaggerated blood pressure response during exercise constitutes a sign of premature cardiovascular stiffening in the setting of uncomplicated hypertension.

In our study the healthy reference group becomes more accurately defined when considering the ankle and exercise blood pressure together, because the discrepancy

between the ABP and brachial exercise systolic blood pressure reveals those patients, who have stenotic changes in conduit vessels, but ankle blood pressure or ABI index is still within the normal limits.

The categorization of our study cohort into five subgroups enabled a logical understanding of the chronological sequence of adverse changes in the ankle blood pressure. In patients with normal ankle, arm and exercise blood pressure (reference group), both total and CVD mortality during the follow-up were low even among persons with an abnormal exercise test. Over the 18-year follow-up (60 266 person-years), the total mortality in the reference group was 125 patients (5.7%) and the mortality due to cardiac causes was only 21 (0.95%) and 78 (3.5%) due to cerebrovascular causes. In other groups the mortality was clearly elevated: total mortality 14–18.5% in groups 2–4 and 46% in group 5. Also the cardiovascular and cerebrovascular mortalities were high: 5.5–6.5 vs, 6.3–7.7 % in groups 2–4 and 13.5–27% in group 5.

7.4 Elevated ankle blood pressure

Our novel finding was that even those persons among whom the elevated ankle blood pressure was the only abnormal finding had 2.7-fold higher multivariate adjusted risk of CDV death and 2.1-fold higher risk of death from any cause than persons with normal brachial, ankle and exercise blood pressures. The elevated ankle blood pressure is one of the earliest signs of the subclinical vascular damage in the arteries. It has an independent value as a marker of subclinical arterial stiffness or atherosclerosis in asymptomatic middle-aged patients.

The aetiology of the elevated ABP was not the topic of this study, but many causes can explain the elevation of ABP. Normally the ABP is 8–10 mmHg higher than the brachial blood pressure. The blood pressure amplifies as it travels distally from the heart, resulting in a progressive increase in systolic blood pressure. The amplification is due to retrograde wave reflection from resistant distal arterioles, which is additive to the antegrade wave. In addition, the hydrostatic pressure in the lower extremities causes increased intraluminal pressure, with increased wall thickening and with unchanged inner radius. Therefore, both reflected waves and changes in vessel wall thickness and consequently stiffness contribute to systolic blood pressure amplification (Aboyans A et al. 2012).

Elevated ABP can be expected, when the systolic blood pressure is elevated or arteries are stiffer. At present, there are no prospective follow-up studies, as to how elevated systolic blood pressure, arterial stiffness, medial calcinosis or occlusive stenotic changes alter the ankle blood pressure over time (Kain K et al. 2013). Also it is unclear, how much the aortic stiffness with attenuated impedance mismatch between aorta and peripheral arteries (enhanced pulse pressure and pulsatility) contributes to ABP elevation.

In the Czech post-MONICA study the increased ABP was associated with increased aortic PWV independently of brachial blood pressure, and the elevated ABP seems more to be a parameter of aortic stiffness than a parameter of lower-extremity artery stiffness which is explained by the loss of buffering function of aorta due to loss of impedance mismatch between aorta and peripheral circulation (Wohlfahrt P et al. 2013). Normally, wave reflection occurs due to arterial stiffness mismatch between the aorta and large muscular arteries and this wave reflection protects microcirculation from the damaging effect of pulsatile energy. According to the MESA study (Ix JH et al. 2010), the association between ABP and aortic stiffness may explain the observed positive association between lower-extremity arterial stiffness and LV mass, which is independent of subclinical atherosclerosis.

On the other hand, in many prospective studies the vascular stiffness seems more likely to be a precursor rather than the result of hypertension (Kaess BM et al. 2012, Najjar SSS et al. 2008, Männistö T et al. 2013) or the functional relationship is bidirectional (Yannoutsos A et al. 2014). Elevated blood pressure may cause vascular damage and accelerated conduit artery stiffening or aortic stiffening increases pressure pulsatility and therefore affects systolic blood pressure.

In summary, elevated ankle blood pressure is likely a reflection of changes in central conduit arteries but also peripheral alterations contribute to the elevated ankle blood pressure. Our results and other prospective studies suggest that increased ABP is linked to increased aortic stiffness and may be a parameter of increased pulsatile energy transmission to the periphery. It is regarded as a direct measure of target organ damage, indicating the occurrence of pathological changes in large artery walls under the action of cardiovascular risk factors.

7.5 Cardiovascular risk prediction

7.5.1 General

The prediction of cardiovascular (CV) risk has many requirements. It must predict future outcomes in prospective studies and add information to established risk markers (Vlachopoulos C 2012). Furthermore, a good biomarker changes predicted risk to a sufficient extent to meaningfully improve risk reclassification in prospective studies. Several computerized methods have been developed for estimating total CV risk (Pyörälä K et al. 1994, D'Agostino RB Sr et al. 2008, Conroy RM et al. 2003, Hippisley-Cox J et al. 2008, Ridker PM et al. 2008, Ridker PM et al. 2007, Woodward M et al. 2007, Vartiainen E et al. 2007), the Framingham Risk Score and European Systematic Coronary Risk Evaluation (SCORE) being among the most widely used. The models typically predict the 10-year risk of a fatal CVD on the basis of gender, age (40–65 years), smoking habits, level of total cholesterol, and systolic blood pressure (SBP) in

persons without previous CVD events. In the FINRISK calculator the coronary risk and stroke risk are calculated separately and cardiovascular risk is evaluated by summing up the coronary risk and stroke risks. HDL-cholesterol and diabetes are also included in the FINRISK model (Vartiainen E et al. 2007).

The strengths and limitations of different risk scoring systems have been reviewed recently (Cooney MT et al. 2009) and considerable overlap remains in estimated risk between those who are affected by a cardiovascular event and those who are not (Berry JD et al. 2012, Schlendorf KH et al. 2012). Predicting a future CV event in individuals who have no prior history of cardiovascular disease has proven difficult when based solely on traditional risk factors and scoring systems (Allan GM, Støvring H et al. 2013, Cavanaugh-Hussey MW et al. 2008, Marma AK et al. 2009). It seems that age alone in the equation integrates a large part of the long term effects of the established risk factors, together with the individual genetic predisposition. The traditional risk factors such as elevated BP, hyperglycemia and raised cholesterol, which fluctuate over time with the follow-up of individual patients, may give only a snapshot at the time of the measurement and not the whole history of arterial ageing. In addition, at every level of traditional risk factor exposure, there is substantial variation in the amount of atherosclerosis and this variation in disease is probably due to genetic and environmental factors.

7.5.2 Subclinical organ damage

The evaluation of subclinical organ damage is useful for improving CVD risk prediction. The easiest measurement may be the PWV, which gives us valuable information about arterial stiffness and reflects true arterial wall damage (Ben-Shlomo Y et al. 2014). It integrates and reflects the long-term effects of the established, as well as of the currently unknown, risk factors on the arterial wall, together with the genetic predisposition of the individual.

Elevated ankle blood pressure, on the other hand, might be a reflection of arterial stiffness as hypothesized in this study and in few other prospective studies (Ix JH et al. 2010, Wohlfahrt P et al. 2013). Like the arterial stiffness, the elevated ABP can be considered as a measure of the cumulative influence of cardiovascular risk factors with aging on the arterial tree. In contrast to the classical ‘circulating’ cardiovascular risk factors, such as BP, glycaemia and lipids, elevated ABP may at least be partly explained by the arterial stiffness and it integrates the long-lasting effects of all identified and nonidentified cardiovascular risk factors and thus may be considered as a ‘tissue’ biomarker. It might be useful for improving CVD risk prediction.

7.6 Strengths and limitations of the study

A strength of our study is the large sample size, the long follow-up period of 18 years, and the prospective design. Furthermore, the Finnish national health care registers allowed analyses of virtually all patients and the loss to follow-up is negligible. The registers also had good accuracy and coverage (Jin YP et al. 2004, Pajunen et al. 2005, Sund R 2012). The ankle blood pressure is measured with the Doppler method which according to a recent statement is the golden standard for the determination of the ABI (Aboyans A et al. 2012).

The representativeness of our study cohort is, however, somewhat limited. The patients were referred to the exercise test by occupational health physicians and thus they do not represent a random sample of the general population. The majority of the patients studied were better educated and had higher than average socioeconomic positions.

Other limitations of the study are related to the collection of clinical data. The ankle blood pressure was measured from one leg only. The blood glucose and total cholesterol were self-reported and only half of the patients knew their glucose value. The persons without a known abnormal cholesterol or glucose values were taken as normal. These values were taken in multivariate analyses, because they were significant predictors of CHD risk as expected. Thus, these limitations of our study should not affect the validity of the findings although some residual confounding cannot be totally excluded. On the other hand, most patients with a diagnosed MI or stroke during the follow-up had received pharmacological therapy or undergone invasive therapeutic procedures and their lifestyle had changed. Such a bias has probably led to an underestimation, rather than an overestimation, of the prognostic significance of elevated ankle blood pressure.

We deliberately did not analyze whether ABP measurement leads to a significant reclassification of CV risk over and above the traditional risk factors. This kind of analyses would very likely have been biased towards positive findings, because the ABP was measured very precisely but data on the traditional risk factors was somewhat less precise and included some residual confounding as described above.

The study was also limited by the lack of stroke subtyping. Subarachnoid hemorrhages were excluded. Intracerebral hemorrhages and ischemic strokes were included, but not subtyped. Generally, approximately 75%–80% of all strokes were of ischemic origin. Also, a gender-specific analysis was not possible because of the small number of events among women.

For the evaluation of dementia our patients did not undergo neuropsychological examinations and we therefore focused only on cognitive decline severe enough to be clinically detected as dementia without any subtyping. The majority of our dementia patients were women, although 66% of our study group were men. It is likely that men had died because of other vascular pathologies before reaching the age where dementia starts to become manifest. The relative risk of dementia because of cardiovascular

disease is attenuated over time as a consequence of the impact of cardiovascular disease on mortality.

7.7 Clinical implications and future research needs

It is easy to measure ABP at the beginning of a normal exercise test. In the present study, an elevated ABP was associated with an increased risk of a cardiovascular event or dementia later in life. These findings were independent of the traditional risk factors but they need to be replicated in other cohorts, preferably including reclassification analyses as well. It remains to be elucidated, how much the new risk marker candidates such as CRP or FMD explain this abnormal finding in a random population. Also, the association between PWV and ABP deserves more detailed research.

In about 6% of our study group we observed a discrepancy between the ankle and exercise blood pressures, which was most likely explained by hemodynamically significant stenotic changes along the conduit vessels. This suggestion needs to be confirmed by other examinations. Also, elevated ABP with inadequate exercise blood pressure reaction may reflect reduced cardiac output caused by CAD.

Low cardiovascular fitness is associated with premature mortality. In this study, in accordance with other studies (Blair SN et al. 1996, Church TS et al. 2004, Sandvik L et al. 1993, Myers J et al. 2002), the low exercise capacity was a more powerful predictor of mortality than the other established risk factors. Half of our unclassifiable group died during the follow-up and most of them belonged to the group with low physical fitness without any specific reason.

In summary, measuring the ankle blood pressure at the beginning of the exercise test is a non-invasive and inexpensive procedure, which provides useful information on the status of the arterial tree and future cardiovascular risk. Wider use of the measurement in clinical work seems warranted.

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ORIGINAL COMMUNICATIONS

Research article

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Ankle blood pressure as a predictor of total and cardiovascular mortality

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Abstract

Background: The ankle blood pressure is commonly used as a ratio to the brachial blood pressure, called ankle-brachial index (ABI). Very few studies have considered the independent value of the ankle blood pressure without indexing it to the brachial blood pressure. We examined the value of ankle blood pressure, together with the exercise blood pressure, as a predictor of cardiovascular (CVD) and total mortality.

Methods: A prospective follow-up study of 3,858 consecutive ambulatory patients (mean age 51 years, 65,9% male) referred to a symptom-limited exercise test between August 1989 and December 1995. The cohort was followed up for all-cause and CVD mortality until December 31, 2004, by record linkage with the National Causes-of-Death Register. The independent value of ankle blood pressure as a predictor of cardiovascular and total mortality was assessed using Cox proportional hazards modelling.

Results: The average follow-up time was 14 years, during which 346 persons died, 108 of them due to CVD. Persons with normal (<140 mmHg) resting brachial blood pressure, ankle blood pressure < 175 mmHg and exercise blood pressure at moderate exercise level \leq 215 mmHg at baseline investigation, had the best prognosis and were taken as the reference category. Among persons with elevated ankle blood pressure (\geq 175 mmHg) but normal or borderline resting brachial pressure and normal exercise blood pressure (\leq 215 mmHg) at moderate exercise level the multivariate-adjusted hazard ratios (HR, 95% confidence interval) for CVD and total mortality were 2.70 (1.52 – 4.80) and 2.13 (1.58 – 2.85), respectively. Similar and equally significant HRs were observed in persons with both elevated ankle blood pressure and elevated exercise blood pressure, as well as in those persons with elevated exercise blood pressure but ankle blood pressure < 175 mmHg.

Conclusion: These results suggest that the ankle blood pressure has an independent value as a marker of arterial stiffness or subclinical atherosclerosis and a risk of future mortality in middle-aged, asymptomatic persons.

Background

There are several established procedures for estimating subclinical atherosclerotic changes in human arteries. Increased carotid intima-media thickness is associated with future cerebrovascular and cardiovascular events [1,2]. Pulse wave velocity is related to arterial wall stiffness, future hypertension and cardiovascular diseases [3,4]. Coronary artery calcium screening is the latest method for evaluating the CVD risk in asymptomatic patients [5,6]. All these methods, however, require sophisticated equipment and a specialized user. Accordingly, they are not well suitable for the screening of early arterial changes in a routine office practice and there is a great need for a simple non-invasive tool that could be used in an office setting to screen for arterial stiffness or subclinical atherosclerosis.

The ankle blood pressure is usually measured in conjunction with the arm blood pressure and the ankle-brachial pressure index (ABI) is calculated. Decreased index is strongly associated with cardiovascular diseases [7-16]. Also elevated ABI value seems to be a significant risk factor of CVD [17,18].

Patients with exaggerated exercise blood pressure reaction have increased cardiovascular disease morbidity compared with those with normal exercise blood pressure reaction [19-22]. It is explained by increased sympathetic tone and structural changes in arteries.

We hypothesized that in the beginning of the arterial stiffening and atherosclerosis the ankle blood pressure may be determined by local factors only, i.e., blood pressure and the elastic properties of arteries. The elevated ankle blood pressure might be one of the earliest signs of adverse changes in the cardiovascular system. Stenotic changes with abnormal ABI are fairly seldom seen in middle-aged persons [13,14]. Ankle blood pressure \leq 175 mmHg but exaggerated elevation of brachial systolic blood pressure at a moderate exercise level reveals those patients in whom stenotic changes along the conduit vessels decrease the ankle blood pressure and this group has to be considered as a separate entity.

Long-term prospective studies on the value of ankle blood pressure in middle-age persons are currently sparse. Therefore, the aim of the present study was to assess the independent value of ankle blood pressure, together with the brachial exercise blood pressure, as a predictor of cardiovascular and total mortality during the average follow-up of 14 years.

Methods

Study population

Subjects for this investigation were derived from a group of 4,038 consecutive ambulatory patients, who underwent symptom-limited bicycle exercise test at the Helsinki Deaconess Institute between August 1989 and December 1995. The patients were referred by occupational health physicians to a symptom-limited exercise test to rule out coronary heart disease and evaluate physical fitness. More precisely, 1,734 were sent for the evaluation of physical fitness, 1,799 for diagnostic testing due to chest pain or shortness of breath, 488 because of suspected arrhythmias and 17 for mixed reasons, mainly for suspicion of exercise-induced asthma. Patients with a history of myocardial infarction, percutaneous coronary angioplasty, coronary artery bypass grafting, congestive heart failure or stroke, were excluded from the analysis. The final study group consisted of 3,858 patients. The study was approved by the Ethical Committee of the National Public Health Institute.

Baseline vascular examination

Brachial blood pressure was measured by trained technicians using the auscultatory method with a standard sphygmomanometer from the left arm of the subject in a supine position after a 5 minute rest. The ankle blood pressure was simultaneously measured from the right leg using a Doppler probe with a mercury sphygmomanometer. If the pulse of the posterior tibial artery was absent, the ankle blood pressure measurements were taken on the dorsalis pedis artery.

Exercise ECG testing and measurement of exercise blood pressure

Exercise testing was conducted on an electronically braked bicycle. The starting load was 50 Watts for men and 40 Watts for women, and the load was increased every 3 minutes by 50 Watts for men and 40 Watts for women. Blood pressure was measured with a sphygmomanometer at 2 minutes at all loads and immediately prior to test termination. Readings were recorded to the nearest 5 mmHg. The 2-minute blood pressure recording at the moderate exercise level (150 W for men and 120 W for women) was used in the analyses. If that level was not reached, blood pressure from the lower level was used. The test was continued until a subject refused to continue, or until the attending physician felt it unsafe to continue. The criteria for myocardial ischaemia during the exercise test were ischaemic changes in ECG defined as ST depression >1.0 mm at 60 ms after the J-point with typical ischaemic complaints.

Other baseline characteristics

Other risk factors assessed at baseline were age, gender, body mass index (BMI), smoking status, medical history,

parental history of early cardiovascular disease, physical working capacity, self-reported history of cardiovascular diseases, total cholesterol and glucose.

Blood pressure groups

Subjects were divided into five groups based on resting ankle and exercise blood pressure at the moderate exercise level (men 150 Watt, women 80 Watt): 1) Reference group, where the resting ankle blood pressure was < 175 mmHg and the exercise blood pressure \leq 215 mmHg; 2) patients with elevated ankle blood pressure (\geq 175 mmHg) but normal exercise blood pressure (\leq 215 mmHg); 3) patients with elevated ankle (\geq 175 mmHg) and elevated exercise blood pressure ($>$ 215 mmHg); 4) elevated exercise blood pressure ($>$ 215 mmHg), but ankle blood pressure <175 mmHg; and 5) patients who could not be classified. Group 4 consists of patients with a discrepancy between the ankle blood pressure and brachial exercise systolic blood pressure, which indicated significant stenotic changes along the conduit vessels. The unclassifiable group could not reach the moderate exercise level because of a specified reason (for example ischaemic heart disease) or an unspecific reason (for example poor physical fitness).

Follow-up procedures

The mortality follow-up data were available up to 15 years (range 12 – 15 years) after the exercise test, until December 31st, 2004. Deaths were ascertained by record linkage of the study data to the National Causes-of-Death Register, on the basis of the personal identification code unique to every resident of Finland. Thanks to the country-wide register, the coverage of the follow-up was 100%.

In the Causes-of-Death Register deaths were coded according to the Ninth (until Dec. 31st, 1995) and Tenth (since the beginning of 1996) versions of the International Classification of Diseases (ICD). The primary endpoint was cardiovascular death, and all-cause mortality was used as a secondary endpoint. ICD-9 codes 410 to 414, 431, 436, 798, 4330A, 4331A, 3339A, 4341A, 4349A, 4376A or ICD-10 codes I20–I25, I46, I61, I63–I64, R96, R98 as the underlying cause of death were taken as cardiovascular deaths. Altogether, 346 persons died during the follow-up, 108 of the deaths were cardiovascular. As a whole, the study consisted of 52,234 person-years of follow-up.

Statistical methods

Data are expressed as mean \pm SD for continuous variables, or counts and proportions for categorical variables. The following cardiovascular risk factors were dichotomized: early parental cardiovascular death (yes or no), self-reported elevated cholesterol ($>$ 6 mmol/l, yes or no), self-reported elevated blood glucose ($>$ 6 mmol/l, yes or no) and current smoking (yes or no). Age, BMI, smoking

(years, packet/day) and blood pressure (mmHg) were handled as continuous variables.

Continuous variables were compared between the blood pressure groups with analysis of variance and proportions with chi-square tests. Univariate associations between different blood pressure indicators were evaluated with Pearson's product-moment correlation coefficients.

Associations between the blood pressure groups and mortality were analyzed using Kaplan-Meier survival curves and log-rank tests. Cox proportional hazard models were used for estimating the multivariate-adjusted independent associations of the blood pressure groups with total and cardiovascular mortality. Results were expressed as hazard ratios (HR) and 95% confidence intervals (CI) compared to the reference group. The basic models were adjusted for age and sex. The larger models were further adjusted for BMI, physical working capacity (metabolic equivalents = METs), self-reported blood glucose and cholesterol, current smoking and early parental history of cardiovascular disease. The statistical analyses were carried out with R (Version 2.3.1).

Results

The mean age at baseline was 50.5 ± 10.0 years (range 15 – 84), and the mean BMI was 26.1 ± 3.8 kg/m². The mean brachial blood pressure was $133.1 \pm 18.7/85.3 \pm 10.9$ mmHg) and pulse 73.8 ± 12.9 /min. The correlation coefficient between the brachial blood pressure at rest and the exercise blood pressure at the moderate exercise level (men 150 Watts, women 80 Watts) was 0.548 ($n = 2,313$, $P < 0.0001$) in men and 0.649 ($n = 1,211$, $P < 0.0001$) in women. The correlation coefficient between the ankle blood pressure and systolic blood pressure at the moderate exercise level was 0.543 ($P < 0.0001$) in men and 0.597 ($P < 0.0001$) in women.

Table 1 compares cardiovascular risk factors in different blood pressure categories at baseline. The ABI differed significantly between the groups being highest in groups 2 and 3 and lowest in groups 4 and 5. The reference group ($n = 2,203$) was younger and leaner. In this group all risk factors were more favourable compared with the other groups. Myocardial ischaemia during exercise was diagnosed in 94 patients. The all-cause mortality during follow-up was 89 patients (4.0%), 20 (0.9%) due to cardiovascular causes.

In patients ($n = 791$) with elevated ankle blood pressure (\geq 175 mmHg) and normal exercise blood pressure the resting brachial blood pressure was normal or slightly elevated: $144 \pm 17/90 \pm 10$ mmHg. Of this group 36% were on cardiovascular medication. In patients without any medication ($n = 510$) the blood pressure was normal or

Table 1: Characteristics of the Study Participants by Ankle Blood Pressure (ABP) and Exercise Blood Pressure (EBP) Group.

	Normal ABP Normal EBP	Elevated ABP and Normal EBP	Elevated ABP and Elevated EBP	Normal ABP and Elevated EBP	Unclassified	p
	n = 2203	n = 791	n = 509	n = 222	n = 133	
Age (years)	47 (10)	55 (9)	54 (7)	51 (9)	59 (10)	0.001*
Male/female	1419/820	447/358	435/87	205/21	105/30	0.001†
Body mass index (kg/m ²)	25.4(4)	26.8 (4)	27.5 (4)	26.9 (4)	25.7 (4)	0.001*
Syst. BP (mmHg)	124 (14)	144 (17)	152 (17)	135 (16)	137 (20)	0.001*
Diast. BP (mmHg)	82 (9)	90 (10)	94 (10)	85 (9)	85 (11)	0.001*
Pulse/min	73 (13)	75 (13)	75 (13)	74 (13)	75 (14)	0.001*
SBP80 (women)	172 (20)	192 (15)	229 (11)	233 (13)	-	0.001*
SBP150 (men)	186 (18)	199 (14)	236 (16)	231 (12)	-	0.001*
SBPMax	193	203	240	236	178.3	0.001*
Ankle blood pressure (mmHg)	150 (17)	194 (14)	198 (18)	157 (14)	141 (37)	0.001*
ABI	1.21 (0.38)	1.31 (0.14)	1.27 (0.17)	1.16 (0.14)	1.03 (0.27)	0.001*
ABI < 0.97 n (%)	66 (3)	0 (0)	0 (0)	22 (1)	39 (29)	0.001†
Self-reported abnormal total cholesterol n (%)	925 (42)	340 (43)	234 (46)	122 (55)	74 (56)	0.001†
Self-reported abnormal glucose n (%)	132 (6)	95 (12)	66 (13)	27 (12)	35 (26)	0.001†
Pos. family history n (%)	793 (36)	324 (41)	188 (37)	95 (43)	69 (52)	0.005†
Pack-years of smoking	9 (11)	9 (12)	13 (14)	14 (13)	20 (16)	0.001*
Current smokers n (%)	308 (14)	71 (9)	71 (14)	36 (16)	51 (38)	0.001†
METs	8.4 (3)	6.6 (2)	7.4 (2)	7.9 (1.9)	4.6 (1.5)	0.001*
Cardiovascular medication n (%)	22 (1)	285 (36)	178 (35)	33 (15)	60 (45)	0.001†
Diagnosed ischemic heart disease n (%)	88 (4)	142 (18)	46 (9)	13 (6)	72 (54)	0.001†
Deaths during follow-up n (%)	88 (4)	119 (15)	56 (11)	22 (10)	60 (45)	0.001†
Cardiovascular deaths during follow-up n (%)	20 (0.9)	40 (5)	20 (4)	9 (4)	23 (17)	0.001†

Mean values (S.D.) or proportions (%), * ANOVA, † χ^2 test

SBP80 = systolic blood pressure at the exercise level of 80 Watts

SBP150 = systolic blood pressure at the exercise level of 150 Watts

SBPMax = maximum systolic blood pressure during exercise

ABI = Ankle Brachial Index

METs = Exercise capacity measured in metabolic equivalents

slightly elevated: $142.2 \pm 15/90.0 \pm 10.1$ mmHg. In this whole group, 116 (14.7%) patients died during the follow-up period, 37 (4.7%) due to cardiovascular causes.

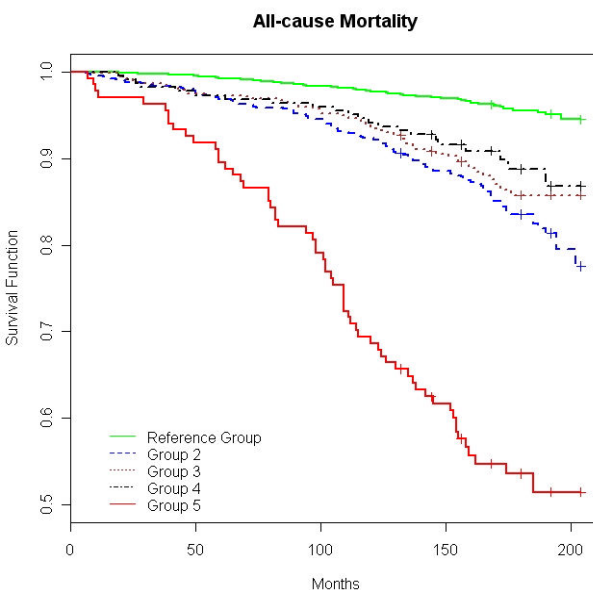
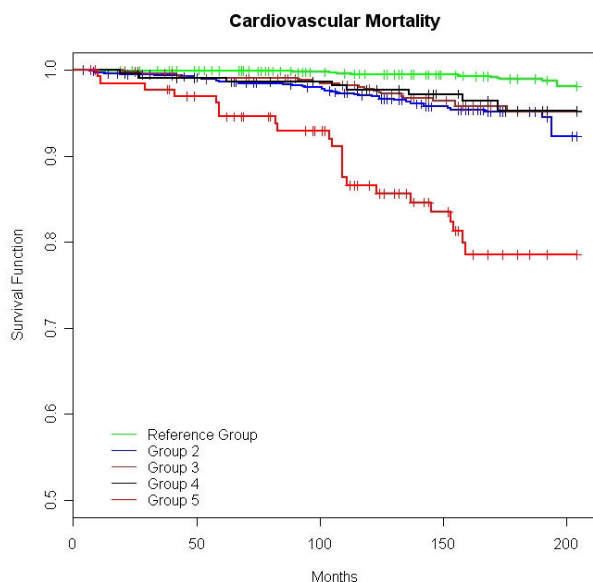
Among patients (n = 509) with elevated ankle blood pressure and elevated exercise blood pressure the male sex dominated. The brachial blood pressure at rest was elevated: $152.8 \pm 17/94.0 \pm 10$ mmHg. Compared with the previous group, BMI and ankle blood pressure were also higher and the smoking history was longer. In patients without any medication (n = 348) the mean blood pressure at rest was elevated: $150.6 \pm 16/93.1 \pm 10$ mmHg. Myocardial ischaemia during exercise was diagnosed in 44 (8.6%) patients. The all-cause mortality in this group was 58 patients (11.4%) and the mortality due to cardiovascular disease was 20 patients (3.9%).

In patients with the discrepancy between the ankle blood pressure and systolic blood pressure (group 4, n = 222) there was no correlation between the ankle blood pressure and exercise blood pressure at moderate level ($r = 0.050$, n = 201, $p = 0.49$) among men and $r = 0.059$, n = 21, $p = 0.80$ among women). Compared with the reference group the ankle blood pressure was a bit higher. The male sex

dominated (201/222) in this group, and smoking was more common than in groups 1 and 2. Fifteen per cent were on cardiovascular medication. Myocardial ischaemia was diagnosed in 14 patients (6.3%), two of them died during the follow-up. The all-cause mortality was 22 patients (9.9%) and the mortality due to cardiovascular causes was 8 (3.6%).

The fifth group (n = 133) was older. They could not tolerate moderate exercise level because of ischaemic heart disease (n = 71) or leg atherosclerotic disease (ABI <0.97, n = 38). Abnormal lung function was observed in 10 patients (oxygen <90%). Almost half of this group (45.2%) died during the follow-up period, 23 (17.3%) due to cardiovascular causes. There were 43 patients with low fitness without any specific reason. Twenty (47%) of them died during the follow-up period, 6 (14%) due to cardiovascular causes. They tended to be current (n = 19) or ex-smokers (n = 7). The male sex dominated (36/43). Nine were on antihypertensive medication.

Figure 1 shows the Kaplan-Meier survival curves for cardiovascular and all-cause mortality in different blood pressure groups. For both endpoints the curves diverge



Reference Group N = 2203	2193	2166	1708	149
Group 2 N = 791	772	747	516	42
Group 3 N = 509	496	484	306	14
Group 4 N = 222	219	213	160	14
Group 5 N = 133	122	105	14	7

Figure 1
Cardiovascular and all-cause mortality by the blood pressure group. Kaplan-Meier survival curves for cardiovascular and all-cause mortality. Log-rank test for the survival difference between the blood pressure groups: $p < 0.0001$ for cardiovascular mortality and $p < 0.0001$ for all-cause mortality. The numbers indicate people remaining in the follow-up at different points in time. All participants were not followed up for 200 months. The reference group consists of patients with normal brachial blood pressure (< 140 mmHg), ankle blood pressure < 175 mmHg and exercise blood pressure ≤ 215 mmHg at the moderate exercise level. Group 2 had elevated ankle blood pressure (≥ 175 mmHg) but normal exercise blood pressure. Group 3 had elevated ankle and exercise blood pressure. Group 4 had ankle blood pressure < 175 mmHg but elevated exercise blood pressure (discrepancy) and group 5 could not be classified because of poor exercise tolerance.

continuously and significantly throughout the 14 years of follow-up.

Compared with group 1, the age and sex-adjusted hazard ratios of CVD and all-cause mortality were significantly elevated in all other groups (Table 2). Further adjustment for traditional risk factors, such as smoking, BMI, parental history of early CVD, self-reported elevated cholesterol and blood glucose attenuated the HRs slightly, but they nevertheless remained clearly significant.

For comparison, we calculated the HRs for the different levels of ankle blood pressure alone (Table 3). Patients with abnormal ABI (<0.97) were kept as their own group. The age and gender adjusted HRs increased linearly with higher ankle blood pressure and were highest in patients with abnormal ABI. Multivariate-adjusted HRs behaved similarly, although they reached statistical significance for all-cause mortality only. Moreover, we calculated the HRs for the usual resting brachial systolic blood pressure, dichotomized at 160 mmHg (<160 mmHg vs ≥160 mmHg). In the age and sex-adjusted model, the HR for CVD death was 1.94 (1.23 – 3.06, p = 0.004). In the larger model the HR was attenuated to 1.6 (1.01 – 2.54, p = 0.04).

Discussion

In the present study, we demonstrated that the ankle blood pressure gives us important information about the status of the arterial tree in middle-aged asymptomatic individuals. The main finding was that even those persons among whom the elevated ankle blood pressure was the

only abnormal finding had 2.7-fold higher multivariate-adjusted risk of CDV death and 2.1-fold higher risk of death from any cause than persons with normal brachial, ankle and exercise blood pressures. This suggests that the measurement of ankle blood pressure could be a relatively simple, inexpensive and non-invasive tool for assessing early, subclinical atherosclerotic changes in young and middle-aged individuals. This finding is consistent with earlier studies suggesting a J-shaped association between ABI and CVD risk [5,17,18].

At least three independent lower-extremity large-vessel characteristics determine the ankle blood pressure: local pressure, elasticity of the vessels and the pulse wave. Arterial stiffness with increased pulse wave velocity and augmented pulse pressure cause a strong cyclic stretching on vascular smooth muscle cells [23-26]. Hypertrophy and structural changes decrease the elasticity of the conduit vessels, and elevated ankle blood pressure is measured. An unanswered question is, when is the ankle blood pressure determined only by local factors, and when do stenotic changes along the conduit vessels begin to have an effect on the peripheral ankle blood pressure. We postulate that this stage is reached when the exercise causes an exaggerated blood pressure reaction but the ankle blood pressure is within the normal limits.

Although the importance of exercise hypertension remains controversial, the majority of recent studies show that an exaggerated systolic blood pressure response to exercise is an independent predictor of future hypertension and CVD mortality [18-20,26-29]. It is associated

Table 2: Hazard Ratios (HR, 95% Confidence Interval (CI)) of Cardiovascular and All-Cause Deaths According to Specified Blood Pressure Groups.

	Model 1			Model 2		
	HR	95% CI	p	HR	95% CI	p
<u>Cardiovascular death</u>						
Group 1	1	(reference)		1	(reference)	
Group 2	3.11	1.79 – 5.41	< 0.0001	2.62	1.49 – 4.62	0.0003
Group 3	2.77	1.48 – 5.16	0.003	2.48	1.33 – 6.62	0.003
Group 4	2.78	1.22 – 6.33	0.02	2.36	1.04 – 5.37	0.02
Group 5	8.45	4.42 – 16.15	<0.0001	4.28	2.07 – 8.87	<0.0001
<u>All-cause death</u>						
Group 1	1	(reference)		1	(reference)	
Group 2	2.40	1.81 – 3.20	<0.0001	2.13	1.59 – 2.85	< 0.0001
Group 3	2.01	1.43 – 2.81	<0.0001	1.80	1.29 – 2.53	<0.0001
Group 4	1.98	1.25 – 3.15	0.003	1.70	1.07 – 2.70	0.03
Group 5	5.92	4.15 – 8.46	<0.0001	3.21	2.15 – 4.79	<0.0001

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, BMI, smoking, early parental cardiovascular disease, exercise capacity measured in metabolic equivalents, self-reported elevated cholesterol and abnormal blood glucose

Please see Table 1 and the Methods-section for the explanation for the blood pressure groups

Table 3: Hazard Ratios (HR, 95% Confidence Interval (CI) of Cardiovascular and All-Cause Deaths in Different Levels of Ankle Blood Pressure (ABP).¹

Ankle Blood Pressure Category (n)	Model 1			Model 2		
	HR	95% CI	p	HR	95% CI	p
<u>Cardiovascular death</u>						
100–150 mmHg (n = 1214)	1	(reference)		1	(reference)	
151–174 mmHg (n = 1082)	1.54	0.85 – 2.79	0.2	1.52	0.83 – 2.78	0.2
175–200 mmHg (n = 1086)	1.71	0.97 – 3.02	0.06	1.73	0.97 – 3.07	0.06
201–300 mmHg (n = 355)	1.98	1.03 – 3.84	0.04	1.77	0.91 – 3.45	0.1
Abnormal (< 0.97) ABI (n = 121)	2.38	1.10 – 5.17	0.03	1.53	0.68 – 3.4	0.3
<u>All-cause death</u>						
100–150 mmHg (n = 1214)	1	(reference)		1	(reference)	
151–174 mmHg (n = 1082)	1.30	0.95 – 1.79	0.1	1.30	0.94 – 1.79	0.2
175–200 mmHg (n = 1086)	1.44	1.06 – 1.95	0.02	1.47	1.08 – 2.00	0.02
201–300 mmHg (n = 335)	1.70	1.18 – 2.43	0.003	1.53	1.06 – 2.21	0.02
Abnormal (0.97) ABI (n = 121)	2.20	1.43 – 3.40	< 0.0001	1.49	1.00 – 2.33	0.02

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, BMI, smoking, early parental cardiovascular disease, exercise capacity measured in metabolic equivalents, self-reported elevated cholesterol and abnormal blood glucose

Please see Table 1 and the Methods-section for the explanation for the blood pressure groups

¹ Persons with low ABI separated as their own group

with insulin resistance [30], hypercholesterolemia [31], carotid atherosclerosis [22] and other target-organ damage [32]. The pathophysiology of exaggerated blood pressure response is not yet fully understood. Two processes have been involved in most studies: increased sympathetic tone and structural changes in the vessels.

The categorization of our study cohort into five subgroups enabled a logical understanding of the chronological sequence of adverse changes in the ankle blood pressure. In patients with normal ankle, arm and exercise blood pressure, both CVD and total mortality during the follow-up were low even among persons with an abnormal exercise test. The elevated ankle blood pressure either with or without elevated exercise blood pressure was significantly associated with CVD mortality and all-cause mortality. It is associated with abnormally high ABI, which has also been found in other studies [17,18].

Patients with elevated exercise blood pressure but ankle blood pressure ≥ 175 mmHg are a more discrete group. With our cut-points (ankle blood pressure ≥ 175 mmHg and exercise blood pressure at moderate exercise level > 215 mmHg) they formed a group in which CVD and all-cause mortality were at the same level as in patients with elevated ankle blood pressure. The discrepancy between the ankle and exercise blood pressures can be explained by hemodynamically significant stenotic changes along the conduit vessels. The poor correlation between the exercise brachial blood pressure and the ankle blood pressure is in accordance with the existence of stenotic

changes. Also, abnormally low ABI was observed in group 4 compared with the reference group.

Normally there is a strong correlation between the arm, ankle and exercise blood pressures as long as the stenotic changes along the conduit vessels are minor. Similar correlation between the systolic blood pressure and maximal or submaximal exercise blood pressure has been found in other studies [27]. Elevated ankle blood pressure alone is also associated with an increased risk for CVD- and overall mortality. Exercise test reveals further those patients, where changes in the conduit vessels decrease the ankle blood pressure and the healthy reference group becomes more accurately defined.

Low cardiovascular fitness is associated with premature mortality. The literature is filled with long-term follow-up studies, conducted in relatively healthy populations [33-36], or focused on clinical patient populations [36], which have indicated, that exercise capacity is a more powerful predictor of mortality than the other established risk factors. One third of our unclassifiable group died during the follow-up and most of them belonged to the group with low physical fitness without any specific reason.

Our study has certain limitations. The patients were referred by occupational health physicians and thus they do not represent a random sample of the general population. The reference group is a predominantly well-educated group. The ankle blood pressure was measured from

one leg only. The blood glucose and total cholesterol were self-reported and only half of the patients knew their glucose value. However, our purpose was not to explain the aetiology of elevated ankle blood pressure but to examine its prognostic value. These limitations of our study should not affect the validity of the findings. Furthermore, most patients with a diagnosed MI during the follow-up had received pharmacological therapy or undergone invasive therapeutic procedures and their lifestyle had changed. Such a bias has probably led to an underestimation, rather than an overestimation, of the prognostic significance of elevated ankle blood pressure.

Conclusion

In the present study we showed that the ankle blood pressure – without indexing to arm blood pressure – has an independent value as a marker of subclinical atherosclerosis in asymptomatic middle-aged patients. The elevated ankle blood pressure is one of the earliest sign of the adverse changes in the arteries. It identifies high-risk individuals and may provide the necessary motivation to promote lifestyle changes. On the other hand, exaggerated exercise blood pressure reaction with normal ankle blood pressure reveals those patients with stenotic changes along the conduit vessels. They are likely to need more detailed investigations and intensive therapy. Thus, measurement of the ankle blood pressure could be an inexpensive and non-invasive tool which helps to assess the CVD risk and to guide the intensity of other examinations and therapies.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

HH: Conceived the idea of the study, investigated the patients, carried out part of the statistical analyses and wrote the first draft of the manuscript.

RP: Took care of the data management and part of the statistical analyses. Contributed to the interpretation of the results and commented on the manuscript with important intellectual content.

VS: Supervised the study. Contributed to the follow-up of the patients and interpretation of the statistical analyses. Commented on the manuscript with important intellectual content.

All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Ankle and exercise blood pressures as predictors of coronary morbidity and mortality in a prospective follow-up study

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Elevated ankle blood pressure (ABP) may be one of the earliest signs of subclinical atherosclerosis. However, its behavior in different degrees of atherosclerotic vascular damage has not been well characterized. We examined the association of ABP and brachial exercise blood pressure with the incidence of future coronary events. A cohort of 3808 consecutive ambulatory persons (mean age 50 years, 34% women), referred to a symptom-limited exercise test and free of cardiovascular events at baseline, was prospectively followed up for 15 years. Altogether, 383 (80 fatal and 303 non-fatal) incident coronary events occurred. Cox proportional hazards models, adjusting for several conventional risk factors, were used to analyse the independent association of ABP with the risk of an incident coronary heart

disease (CHD) event. Persons with normal ankle, brachial resting and brachial exercise blood pressures were taken as the reference group. Other groups were formed on the basis of ankle and exercise blood pressures and compared with the reference group. Even in persons among whom the elevated ABP was the only abnormal finding, the multivariate adjusted hazard ratio (HR) of a future CHD event was significantly elevated (HR = 1.60, 95% confidence interval 1.20–2.14, $P < 0.0001$). In general, the HRs were higher for fatal events than for non-fatal events. The measurement of ABP could be an inexpensive and non-invasive tool to detect elevated risk of a CHD event.

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Keywords: myocardial infarction; CHD; blood pressure; ankle brachial index; ABP

Introduction

The ankle blood pressure (ABP) has usually been indexed to brachial blood pressure to form the ankle-brachial blood pressure index (ABI). Low values of ABI (< 0.95) signal advanced peripheral artery disease and significantly elevated risk of a major cardiovascular disease (CVD) event.^{1–7} Stenotic changes leading to abnormally low ABI are, however, relatively rare in middle-aged persons.^{4,5} Furthermore, also elevated ABI (> 1.40) or high ABP may be associated with increased risk, although the literature is somewhat conflicting.^{7–11} The behavior of the ABP in different degrees of atherosclerotic vascular damage has not been well characterized and very few studies have attempted to use the ABP as a risk marker without indexing it to the brachial blood pressure.

In the beginning of the atherosclerotic process and arterial stiffening the ABP is determined by local factors only, that is, blood pressure and the elastic properties of arteries, and the elevated ABP may be one of the earliest signs of subclinical vascular damage.¹² More advanced atherosclerosis is propagated from the arterial wall to the arterial lumen and stenotic changes along the conduit vessels decrease the ABP. This step is reached when physical exercise causes an exaggerated blood pressure reaction while the ABP is normal. Accordingly, we hypothesized that categorizing the persons in a logical manner on the basis of the ABP and exercise brachial blood pressure could provide an even more sensitive tool than ABI for detecting early arterial changes.

We have followed up for an average of 15 years a cohort of 3808 middle-aged persons (mean age 50 years, range 15–84 years, 34% women) whose ABP and exercise brachial blood pressure, as well as physical working capacity, were measured at baseline. The aim of this study was to assess the association of ABP, together with the resting and exercise brachial blood pressures, with coronary morbidity and mortality during the follow-up.

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Methods

Study population

Subjects for this investigation were derived from a group of 4038 consecutive ambulatory persons, who underwent symptom-limited bicycle exercise testing at the Deaconess Institute in Helsinki between August 1989 and December 1995. The persons were referred by occupational health physicians to a symptom-limited exercise testing to rule out coronary heart disease (CHD) and evaluate physical fitness. Persons with a documented history of myocardial infarction (MI), percutaneous coronary angioplasty, coronary artery bypass grafting or stroke were excluded from the analysis. The patients with a positive ischaemic finding in the exercise test but no history of a hard cardiovascular event were included in the follow-up and analyses. The final study group consisted of 3808 persons. Of them, 759 persons were under medication and the antihypertension medication was the most important drug therapy (412 used β -blockers, 48 diuretics and 185 used angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers). In all, 52 persons had medication for diabetes.

The study was approved by the Ethical Committee of the National Public Health Institute.

Baseline vascular examination

Brachial blood pressure was measured by trained technicians using the auscultatory method with a standard mercury sphygmomanometer from the left arm of the subject in a supine position after a 5 min rest. The ABP was simultaneously measured from the right leg using a Doppler probe with a mercury sphygmomanometer. The posterior tibial artery was used, and if absent, the ABP measurements were taken from the dorsalis pedis artery.

Exercise testing was conducted on an electrically braked bicycle. The starting load was 50 W for men and 40 W for women, and the load was increased every 3 min by 50 W for men and 40 W for women. Blood pressure was measured with a sphygmomanometer at 2 min at all loads and immediately before test termination. Readings were recorded to the nearest 5 mm Hg. The test was continued until the subject refused to continue, or until the attending physician felt it unsafe to continue. The criteria for myocardial ischaemia during the exercise test were ischaemic changes in electrocardiogram defined as ST depression >1.0 mm at 60 ms after the J-point with typical ischaemic complaints (chest pain or shortness of breath).

Other baseline characteristics

Other risk factors assessed at baseline were age, gender, body mass index (BMI), smoking status, medical history, family history of early cardiovascular disease (under 60 years), physical working

capacity, self-reported history of cardiovascular diseases, total cholesterol and glucose. This information was collected by the attending physician (HH) by interviewing the patient before the exercise test. Height and weight were asked by nurses and BMI was calculated.

Blood pressure groups

Subjects were divided into five groups based on the ABP at rest and exercise brachial blood pressures at moderate exercise level (men 150 W, women 80 W): (1) normal (reference) group, in which both ankle and exercise brachial blood pressures were within normal limits; (2) persons with elevated ABP (≥ 175 mm Hg) but normal exercise brachial blood pressure (≤ 215 mm Hg); (3) persons with elevated ankle (≥ 175 mm Hg) and exaggerated exercise brachial blood pressure (> 215 mm Hg); (4) exaggerated exercise brachial blood pressure (> 215 mm Hg), but normal ABP (< 175 mm Hg); and (5) persons who could not be classified. Groups were constructed because they made sense pathophysiologically and because the ABP has a U-shaped association with the risk of a coronary event and cannot therefore be analysed as a continuous variable. As there are no established reference values for the ABP or the brachial exercise blood pressure, we chose our cut-points (175 and 215 mm Hg) arbitrarily to create groups of reasonable size. Group 4 consisted of persons with a discrepancy between the ankle and exercise brachial blood pressures, which suggested haemodynamically significant stenotic changes along the conduit vessels. The group 5 could not tolerate the moderate exercise level (men 150 W and women 80 W) because of specified reason (for example, ischaemic heart disease) or unspecific reason (for example, poor physical fitness). This group 5 was included in the analyses for completeness and secondly to examine the risk associated with poor physical fitness.

Follow-up and definition of outcomes

The end point of the study was a major coronary event, that is, coronary death or first non-fatal coronary event, including MI, percutaneous coronary angioplasty or coronary artery bypass graft surgery. The mortality and morbidity follow-up data were available up to 15 years (range 12–15 years) after the exercise test, until 31 December 2006. Every resident of Finland has a unique personal identification code that was used for record linkage of the study data with nation-wide, computerized health-care registers. Deaths were ascertained from the national Causes-of-Death Register. Non-fatal MIs and revascularizations were identified from the national Hospital Discharge Register. These registers cover all deaths and hospitalizations in Finland. Thus, the coverage of follow-up was 100% for events that occurred in Finland.

The 9th version of the International Classification of Diseases (ICD-9) was used in Finland for coding of causes of death and hospitalizations until 31 December 1995, and the 10th version (ICD-10) after that. Revascularizations were coded according to the Nordic Medico-Statistical Committee (NOMESCO) Classification.¹³ From the Causes of Death Register, we took coronary deaths events with the ICD-9 codes 410–414 or 798 or the ICD-10 codes I20–I25, I46, R96 or R 98 as the underlying cause of death. From the Hospital Discharge Register, we took non-fatal MI events hospitalizations with the ICD-9 codes 410 or 4110, or the ICD-10 codes I21–I22 and I20.0.

Altogether, 383 coronary events were observed during the follow-up. Of them, 80 were fatal and 303 non-fatal. As a whole, the study consisted of 52 985 person-years of follow-up.

Statistical methods

Data are expressed as mean \pm s.d. for continuous variables, or counts and proportions for categorical variables. The following cardiovascular risk factors were dichotomized: early parental cardiovascular death (yes or no), self-reported elevated cholesterol (>6 mmol l⁻¹, yes or no), self-reported elevated blood glucose (>6 mmol l⁻¹, yes or no) and current smoking (yes or no). Age, BMI, smoking (years, packet day⁻¹) and blood pressure (mm Hg) were handled as continuous variables. Student's *t*-tests or Mann–Whitney *U*-tests were used for comparisons of normally distributed and skewed continuous variables, between persons with and without a coronary event during the follow-up. Categorical variables were compared using χ^2 -tests.

Associations between the blood pressure groups and coronary mortality and morbidity (first events) were analysed using Kaplan–Meier curves and log-rank tests. Cox proportional hazard models were used for estimating the multivariate-adjusted independent associations of the blood pressure groups with the risk of a coronary event. Results were expressed as hazard ratios (HR) and 95% confidence intervals (CI) compared with the 'normal' group. The basic models were adjusted for age and sex. The larger models were further adjusted for BMI, physical working capacity (METs), self-reported blood glucose and cholesterol, current smoking and early parental history of cardiovascular disease. The proportional hazards assumption was examined graphically and was found to be valid. A gender-specific analysis was also performed to evaluate gender differences.

The statistical analyses were carried out with R (Version 2.6.2).

Results

Baseline characteristics and follow-up events

Differences in baseline characteristics between persons with and without a CHD event during the

follow-up are presented in Table 1. Persons with a CHD event were older, especially women (62 years). In persons without a CHD event, almost all risk factors were more favourable compared with the CHD event group. A total of 383 coronary events occurred during the follow-up of 16 years. There were 80 deaths due to CHD, 124 non-fatal MIs, 57 percutaneous coronary angioplasties and 122 persons with coronary artery bypass grafting.

Table 2 compares cardiovascular risk factors in different blood pressure groups. The reference group was younger and all risk factors were more favourable compared with the other groups. In the reference group, 4% of individuals had positive exercise test without a CHD event in the follow-up.

Figures 1 and 2 show the Kaplan–Meier curves of the five blood pressure groups for all CHD events and fatal CHD events. The curves clearly show the best prognosis of the group with normal ankle and exercise brachial blood pressures and the worst prognosis of the group with poor physical performance (group 5). The curves of the other groups (groups 2–4) are very close to each other between the two extremes.

Multivariate models

The most significant predictors of CHD event were gender (HR, women compared with men, 0.27, 95% CI 0.21–0.36, $P < 0.0001$), age (HR 1.05, 95% CI 1.04–1.07, $P < 0.0001$), systolic blood pressure (HR 1.01, 95% CI 1.01–1.02, $P < 0.0001$), physical performance (METs, HR 0.78, 95% CI 0.73–0.83, $P < 0.0001$), self-reported elevated cholesterol (HR 1.30, 95% CI 1.06–1.59, $P = 0.01$) and pack-years of smoking (HR 1.02, 95% CI 1.01–1.02, $P < 0.0001$), when positive family history and self-reported elevated blood glucose were adjusted for.

The age- and sex-adjusted and the multivariate adjusted HRs of a CHD event in the different blood pressure groups are shown in Table 3. Compared with the reference group, the most elevated risk was seen in group with poor physical performance (group 5). The persons with elevated ABP without exaggerated exercise brachial blood pressure and normal or slightly elevated resting brachial blood pressure ($144 \pm 16/90 \pm 10$ mm Hg) had 2.03-fold risk of a CHD event compared with the reference group. Further adjustment for traditional risk factors, such as smoking, BMI, parental history of early CVD, self-reported elevated cholesterol and blood glucose attenuated the HR slightly, but it nevertheless remained clearly significant (1.60-fold). The persons with elevated ABP and exaggerated brachial exercise blood pressure at a moderate exercise level had a 1.89-fold risk in the basic model and 1.60-fold risk in the larger model compared with the reference group. In this group, the resting brachial BP was also elevated ($153 \pm 17/94 \pm 10$ mm Hg). In persons with a discrepancy between the ankle and exercise brachial blood pressures, that is, normal ABP and elevated exercise brachial blood pressure (group 4), the risk of a future coronary event was even higher (2.34-fold

Table 1 Baseline characteristics of participants with and without incident CHD event during the follow-up

	No CHD event, n = 3425	CHD event, n = 383	P-value
Age (years)	50 (10)	56 (9)	0.0001 ^a
Men/women, n (%)	2224 (65)/1201 (35)	304 (79)/79 (21)	0.0001 ^b
Body mass index (kg m ⁻²)	26.0 (4)	26.9 (4)	0.0001 ^a
Systolic blood pressure (mm Hg)	132 (18)	142 (19)	0.0001 ^a
Diastolic blood pressure (mm Hg)	85 (11)	88 (10)	0.0001 ^a
Pulse per min	74 (13)	73 (12)	NS
SBP80 (women)	181 (25)	199 (21)	0.0001 ^c
SBP150 (men)	200 (27)	213(28)	0.0001 ^c
SBPMax	203 (28)	206 (31)	0.05 ^a
Ankle blood pressure (mm Hg)	165 (27)	172 (33)	0.0001 ^a
ABI	1.21 (0.22)	1.18 (0.2)	0.01 ^a
Current smokers, n (%)	543 (15)	103 (28)	0.0001 ^b
Self-reported abnormal total cholesterol, n (%)	1245 (36)	184 (48)	0.0001 ^b
Self-reported abnormal blood glucose, n (%)	236 (7)	57 (15)	0.0001 ^b
Positive family history, n (%)	1266 (37)	165 (43)	0.002 ^b
METs	7.9 (3)	6.5 (2)	0.0001 ^a
<i>Blood pressure groups</i>			
Group I (reference)	2072 (60%)	106 (28%)	
Group II	665 (19%)	107 (28%)	
Group III	428 (13%)	69 (17%)	
Group IV	188 (6%)	38 (10%)	
Group V	72 (2%)	63 (16%)	0.0001 ^b

Abbreviations: ABI, ankle-brachial index; CHD, coronary heart disease; NS, not significant.

Data are mean (s.d.) or *n* and proportions (%).

SBP80: systolic blood pressure at the exercise level of 80 W.

SBP150: systolic blood pressure at the exercise level of 150 W.

SBPMax: maximum systolic blood pressure during exercise.

METs: physical working capacity in metabolic equivalents

Please see the Methods section for explanation for the blood pressure groups.

^aStudent's *t*-test.

^b χ^2 -Test.

^cMann-Whitney *U*-test.

Table 2 Baseline characteristics of participants by the ankle and exercise blood pressure group

	Group 1	Group 2	Group 3	Group 4	Group 5	P-value
	n = 2179	n = 772	n = 497	n = 226	n = 135	
Age (years)	47 (10)	55 (9)	54 (7)	51 (9)	59 (10)	0.0001 ^a
Male/female	1379/800	428/344	417/80	206/20	101/34	0.0001 ^b
Body mass index (kg m ⁻²)	25.4 (4)	26.8 (4)	27.5 (4)	26.9 (4)	25.7 (4)	0.0001 ^a
Systolic blood pressure (mm Hg)	124 (14)	144 (17)	152 (17)	135 (16)	137 (20)	0.0001 ^a
Diastolic blood pressure (mm Hg)	81 (9)	90 (10)	94 (10)	85 (9)	85 (11)	0.0001 ^a
Ankle blood pressure (mm Hg)	150 (17)	194(14)	198 (18)	157 (14)	141 (37)	0.0001 ^a
Antihypertensive medication (n, %)	214 (10)	241 (31)	133 (27)	27 (12)	53 (39)	0.0001 ^b
Elevated cholesterol (n, %)	707 (32)	336 (43)	227 (46)	106 (47)	53 (40)	0.0001 ^b
DM (n, %)	91 (4)	92 (12)	65 (13)	18 (8)	24 (18)	0.001 ^b
Pack-years of smoking	9 (11)	9 (12)	13 (14)	14 (13)	20 (16)	0.0001 ^a

Data are mean (s.d.) or *n* and proportions (%).

Please see the Methods section for the explanation for the blood pressure groups.

^aAnalysis of variance.

^b χ^2 -Test.

in the age and sex adjusted model and 1.97-fold in the multivariate adjusted model). The resting brachial blood pressure was normal or slightly elevated ($135 \pm 15/86 \pm 9$ mm Hg).

In general, the HRs were higher for fatal than for non-fatal CHD events. The persons with poor physical performance (group 5) had the highest risk for fatal outcome (18.0-fold in the basic model and

5.1-fold in the larger model). In groups 2–4, the risk of CHD death was about 3.8- to 4.6-fold in the basic model and about 3.1- to 3.6-fold in the larger model. In addition, the risk of a non-fatal CHD event was significant for all groups in both models.

For comparison, we also calculated the HRs for the usual brachial systolic blood pressure, for exercise brachial blood pressure and for ABP

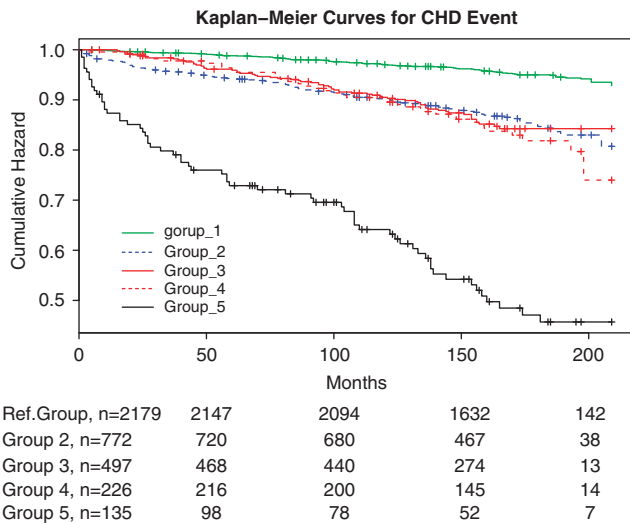


Figure 1 CHD mortality and morbidity (event) according to the specified blood pressure group. Kaplan–Meier curves for all CHD events. Log–rank test for the difference between the blood pressure groups: $P < 0.0001$. The numbers indicate people remaining in the follow-up at different points of time. All participants were not followed up for 200 months. The reference group consists of persons with normal brachial pressure (< 140 mm Hg), ABP < 175 mm Hg and exercise blood pressure ≤ 215 mm Hg at the moderate exercise level. Group 2 had elevated ABP (≥ 175 mm Hg) but normal exercise blood pressure. Group 3 had elevated ankle and exercise blood pressure. Group 4 had ABP < 175 mm Hg but elevated exercise blood pressure (discrepancy) and group 5 could not be classified because of poor exercise tolerance.

alone. The resting brachial systolic blood pressure was dichotomized at 160 mmHg (≤ 160 vs > 160 mmHg). In the basic model, that is, adjusted

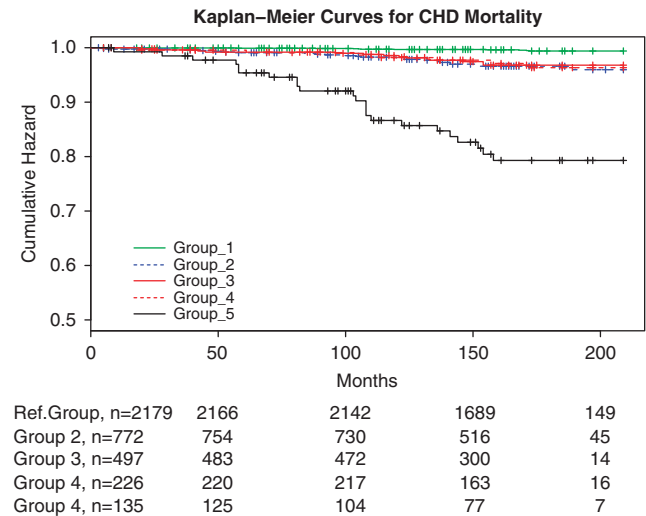


Figure 2 CHD mortality according to the specified blood pressure group. Kaplan–Meier curves for fatal CHD events. Log–rank test for the difference between the blood pressure groups: $P < 0.0001$. The numbers indicate people remaining in the follow-up at different points of time. Blood pressure groups as in Figure 1.

Table 3 Hazard ratios (HR, 95% confidence interval (CI)) of CHD mortality and morbidity according to the specified blood pressure group

	Model 1			Model 2		
	HR	95% CI	P-values	HR	95% CI	P-values
<i>Non-fatal CHD events (n = 3723, number of events = 303)</i>						
Group I	1	(Reference)		1	(Reference)	
Group II	1.79	1.32–2.43	0.0004	1.39	1.02–1.91	0.02
Group III	1.71	1.22–2.40	0.003	1.46	1.04–2.05	0.03
Group IV	2.11	1.39–3.20	0.0005	1.79	1.18–2.73	0.007
Group V	5.64	3.76–8.44	< 0.0001	2.55	1.60–4.08	< 0.0001
<i>Fatal CHD events (n = 3803, number of events = 80)</i>						
Group I	1	(Reference)		1	(Reference)	
Group II	4.32	2.09–8.93	< 0.0001	3.63	1.73–7.62	0.0003
Group III	3.78	1.70–8.43	0.003	3.06	1.36–6.86	0.003
Group IV	4.61	1.77–12.0	0.003	3.60	1.37–9.44	0.003
Group V	18.03	8.21–39.60	< 0.0001	5.05	4.03–24.6	< 0.0001
<i>All CHD events (n = 3803, number of events = 383)</i>						
Group I	1	(Reference)		1	(Reference)	
Group II	2.03	1.54–2.68	< 0.0001	1.60	1.20–2.14	< 0.0001
Group III	1.89	1.38–2.57	< 0.0001	1.60	1.18–2.19	0.003
Group IV	2.34	1.60–3.42	< 0.0001	1.97	1.34–2.89	0.0003
Group V	6.74	4.78–9.50	< 0.0001	3.27	2.19–4.87	< 0.0001

Abbreviation: CHD, coronary heart disease.

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, body mass index, smoking, early parental cardiovascular disease and physical working capacity (METs), self-reported elevated cholesterol and abnormal blood glucose.

Please see the Methods section for explanation for the blood pressure groups.

for age and sex only, the HR for a CHD event was 1.23 (0.98–1.55, $P=0.07$). In the larger model, the HR was 1.27 (1.00–1.60, $P=0.05$). The same comparison was repeated using the fatal CHD event as the outcome. In the basic model, the HR was 1.16 (0.70–1.93, $P=0.6$) and in the larger model the HR was 1.20 (0.71–2.04, $P=0.50$). In persons with elevated exercise blood pressure (>215 mm Hg) at the moderate exercise level, the HRs for fatal or non-fatal CHD event were also elevated, but not significant in either model.

When analysing the ABP alone, we considered four mutually exclusive categories: (1) ABP <175 mm Hg was taken as the 'normal' or reference category; (2) ABP between 175–215 mm Hg was taken as the 'moderately elevated ABP' category; (3) ABP >215 mm Hg was taken as the 'high ABP' category; and (4) person with abnormal ABI (<0.97) were considered as their own category. In persons with moderately elevated ABP, the HRs for fatal and non-fatal CHD event did not reach statistical significance in any of the models (data not shown). In persons with high ABP, the HR for a fatal and non-fatal CHD event was significantly elevated in the basic model only, 2.11 (1.05–4.27, $P=0.04$) and 1.49 (1.12–1.98, $P=0.006$). Also, in persons with abnormal ABI, the HR for a fatal and non-fatal CHD event was significant in the basic model only, 3.34 (1.34–8.31, $P=0.01$) and 1.91 (1.24–2.96, $P=0.004$).

Discussion

The main finding of this study was that the elevated ABP, when considered together with exercise blood pressure, was a significant independent predictor of incident CHD event even in persons with normal resting blood pressure. On the other hand, persons with normal ankle and exercise brachial blood pressure had clearly the best prognosis and only 5% of them had a CHD event during the 15-year long follow-up. In groups 2–4, 12–14% of persons had a CHD event during the follow-up. In our earlier study, we have shown that the same categories of ankle and exercise brachial blood pressure predicted total and cardiovascular mortality.¹² The novel features of this study were the specific focus on CHD, including both morbidity and mortality, and the addition of two more years of follow-up time. This study extended the earlier observations by showing that the differences in mortality between the blood pressure groups were largely due to CHD. The HRs for non-fatal CHD events were consistent with those of the fatal events, although somewhat weaker. For comparison, we also provided a separate analysis on the ABP alone as a predictor for CHD.

At least three separate lower-extremity large-vessel characteristics determine the ABP: local blood pressure, elastic properties of arteries and

pulse wave pressure. Elevated ABP is measured when the arterial stiffness and medial calcification have an influence on the compressibility of the arteries. The interpretation of the ABP measurement is, however, complicated by stenotic changes along the conduit vessels. Although stenotic changes with abnormal ABI are fairly seldom seen in middle-aged persons,^{4,5} the influence becomes substantial in elderly persons. We postulate that the discrepancy between the ankle and exercise blood pressures, that is, high exercise brachial blood pressure and normal or low ABP, disclose the persons with haemodynamically significant stenotic changes along the conduit vessels.

The categorization of our study cohort into five subgroups enabled a logical understanding of the chronological sequence of adverse changes in the ABP. In persons with normal ankle, resting brachial and exercise brachial blood pressures the CHD events were rare, even among persons with a positive exercise test. The elevated ABP either with or without elevated exercise brachial blood pressure was significantly associated with the risk of any CHD event and especially with CHD mortality. The elevated ABP might be one of the earliest signs of subclinical vessel damage, because even those persons among whom the elevated ABP was the only abnormal finding, had 1.6-fold higher multivariate—adjusted risk of a CHD event than persons with normal resting brachial, ankle and exercise brachial blood pressure. Persons with exaggerated exercise blood pressure but normal ABP are a more discrete group. With our cut-points (ABP <175 mm Hg and exercise blood pressure at moderate exercise level >215 mm Hg) they formed a group, in which the risk of a CHD event was 2.0- to 2.3-fold compared with the reference group. Discrepancy between the ankle and exercise blood pressures is a logical step in the progression of atherosclerosis and peripheral artery disease.

Low cardiovascular fitness is associated with premature mortality. The literature is filled with long-term follow-up studies, conducted in relatively healthy populations, or focused on clinical patient populations, which indicate that exercise capacity is a more powerful predictor of mortality than the other established risk factors.^{14–17} Our results are in agreement with this literature, as 44% of our unclassifiable group had a CHD event during the follow-up.

The representativeness of our study cohort is somewhat limited. The persons were referred to the exercise test by occupational health physicians and thus the persons do not represent a random sample of the general population. The study participants were better educated and had higher than average socioeconomic positions. Other limitations of the study are related to the collection of clinical data. The ABP was measured from one leg only. The blood glucose and total cholesterol were self-

reported and only half of the persons knew their glucose value. The information on cholesterol and glucose levels was obtained by an interview of a doctor, which gives them some reliability. These values were taken in multivariate analyses, because they were significant predictors of CHD risk as expected. Persons with a CHD event during the follow-up had a more favourable risk factor profile than those without. These differences were controlled for in multivariate models, but some residual confounding cannot be totally excluded. Moreover, a gender-specific analysis was not possible among women because of the small numbers of events but nothing in the results suggested that the effects of the blood pressure groups would differ by gender. These limitations of the study should not affect the validity of the findings on the prognostic value of elevated ABP. Furthermore, most persons with a diagnosed MI during the follow-up had received pharmacological therapy or undergone invasive therapeutic procedures and their lifestyle had changed. Such a bias has probably led to an underestimation, rather than an overestimation, of the prognostic significance of elevated ABP.

In this paper, we showed that the elevated ABP—without indexing to resting brachial blood pressure—has an independent value as a marker of CHD risk probably because it indicates subclinical vascular damage, that is, arterial stiffness or early atherosclerosis, in asymptomatic middle-aged persons. It identifies high-risk individuals and may provide the necessary motivation to promote lifestyle changes. On the other hand, exaggerated exercise blood pressure reaction with normal ABP reveals those persons with stenotic changes along the conduit vessels. They are likely to need more detailed investigations and intensive therapy. Thus, measurement of the ABP could be an inexpensive and non-invasive tool, which helps to assess the CHD risk and to guide the intensity of other examinations and therapies.

What is known about this topic

- Low and high ankle-brachial index is associated with increased cardiovascular disease morbidity.
- The ankle blood pressure is elevated in patients with abnormally high ankle-brachial index.

What this study adds

- This prospective follow-up study further clarifies the clinical value of high ankle blood pressure.
 - Elevated ankle blood pressure—without indexing to resting brachial blood pressure—has an independent value as a marker of subclinical vascular damage, that is, arterial stiffness or early atherosclerosis in asymptomatic middle-aged persons.
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Conflict of interest

The authors declare no conflict of interest.

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Research Article

Ankle Blood Pressure and Pulse Pressure as Predictors of Cerebrovascular Morbidity and Mortality in a Prospective Follow-Up Study

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Background and Objective. We examined the association of elevated ankle blood pressure (ABP), together with exercise blood pressure, with incident cerebrovascular (CV) morbidity and mortality in a prospective follow-up study of 3,808 patients. The results were compared with pulse pressure, another indicator of arterial stiffness. *Methods.* Patients with normal ankle and exercise brachial blood pressures were taken as the reference group. Pulse pressure was considered as quartiles with the lowest quartile as the reference category. *Results.* A total of 170 subjects had a CV event during the follow-up. Multivariate adjusted hazard ratio of a CV event was 2.24 (95% CI 1.43–3.52, $P < .0001$) in patients with abnormal ABP. The pulse pressure was significant only in the model adjusted for age and sex. *Conclusion.* The risk of a future CV event was elevated already in those patients among whom elevated ABP was the only abnormal finding. As a risk marker, ABP is superior to the pulse pressure.

1. Introduction

High ankle blood pressure (ABP) might be an emerging risk marker for early subclinical damage of arterial vessels evaluated as elevated ankle blood pressure alone [1, 2] or in conjunction with the elevated ankle brachial index (ABI) [3–5]. The high ABP or high ABI provides an indication of arterial stiffness or atherosclerosis of the vessel wall whereas the low ankle pressure or low ABI is indicative of advanced atherosclerosis, which has reached the point where the blood flow is impeded. Several studies have demonstrated that there is a nonlinear, U-shaped association between the ankle brachial index and total mortality or cardiovascular events [4–10]. On the other hand, while the normal ABI does not exclude significant peripheral arterial disease [6, 11, 12] the ABP alone could be useful in evaluating early vascular changes.

The pulse pressure (PP) has been used as a crude indicator of arterial stiffness [13–17]. The increased PP predicts

dementia [18] and cardiovascular mortality [15], acting more on coronary than cerebrovascular (CV) vessels [19]. In hypertensive subjects with high PP, stroke mortality is increased [20, 21]. In many recently published papers the central PP is more closely related to vascular damage than the peripheral PP [13, 22–26], and the peripheral pressure does not necessarily accurately reflect the central pressure. The difference between central and peripheral PP is dependent on age, height, and heart rate making the evaluation of aortic pulse pressure from a peripheral pulse pressure difficult.

Elevated ABP may provide a pivotal opportunity to identify persons at high risk of stroke or TIA. Accordingly, the main aim of the present study was to assess the utility of ABP, together with exercise brachial BP, as a predictor of CV events in a prospective setting. The second aim was to investigate whether the elevated ABP predicts CV events better than the pulse pressure. Both measurements reflect aortic stiffness. We hypothesized that the ABP would be superior to the pulse pressure for screening purposes.

2. Material and Methods

This prospective follow-up study was initiated in August 1989. The methods of baseline data collection have been described in our previous paper [1]. The subjects were derived from a group of 4,038 consecutive ambulatory patients who underwent a symptom-limited bicycle exercise test at the Deaconess Institute between August 1989 and December 1995. Patients with a history of cardiovascular disease (including those with a history of cerebrovascular events) at baseline investigation were excluded from the analyses, and the final study group consisted of 3,808 patients. The study was approved by the Ethical Committee of the National Public Health Institute of Finland.

The ankle and brachial blood pressures were obtained simultaneously after a 5 min rest in supine position using the Doppler sonography for the ABP and the standard mercury sphygmomanometer for the left arm blood pressures. Subjects were divided to five groups based on the ABP at rest and exercise blood pressures (EBPs) at a moderate exercise level (men 150 Watts, women 80 Watts) as shown in the flow chart (Figure 1).

The reference group consisted of “normal” patients with normal ABP (<175 mmHg) and normal systolic EBP (≤ 215 mmHg). Group 2 consisted of patients with elevated ABP (≥ 175 mmHg), but normal EBP. Group 3 had elevated ABP and exaggerated EBP (> 215 mmHg). Patients in group 4 had elevated EBP, but the ABP was normal. The discrepancy between the ABP and EBP indicates significant atherosclerotic changes in conduit vessels. Group 5, the unclassifiable group, consisted of patients, who could not tolerate the moderate exercise level.

The follow-up was 16 years, until the end of 2007 using record linkage of the study data with the National Hospital Discharge Register and the National Causes of Death Register. The endpoint was a major CV event, that is, death due to CV, nonfatal stroke, or a transient ischemic attack (TIA). The 9th (until 31.12.1995) and 10th versions of the International Classification of Diseases (ICD-9 and ICD-10) were used for coding of causes of death and hospitalizations. We took as CV events the ICD-9 codes 431, 436, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, and 435 or the ICD-10 codes I61, I63-I64, G45. These registers cover all deaths and hospitalizations in Finland. Thus, the coverage of follow-up was 100% for symptomatic stroke events leading to hospitalization or death in Finland. It is however likely that all TIAs have not been hospitalized and those treated on an ambulatory basis are not identified as CV events in the present study. Altogether, 170 CV events were observed during the follow-up. Of them, 31 were fatal. As a whole, the study consisted of 53,044 person-years of followup.

2.1. Statistics. Data are expressed as mean \pm SD for continuous variables or counts and proportions for categorical variables. The following cardiovascular risk factors were dichotomized: early parental cardiovascular death (yes or no), self-reported elevated cholesterol (> 6 mmol/l, yes or no), self-reported elevated blood glucose (> 6 mmol/l, yes or no), and current smoking (yes or no). Age, BMI,

smoking (years, packet/day), and blood pressure (mmHg) were handled as continuous variables. Student's *t*-tests were used for comparisons of normally distributed variables, between persons with and without a CV event during the follow-up. Categorical variables were compared using chi-square tests.

Associations between the blood pressure groups, and CV mortality and morbidity (first events) were analyzed using Kaplan-Meier curves and log-rank tests. Cox proportional hazards models were used for estimating the multivariate-adjusted independent associations of the blood pressure groups or the quartiles of pulse pressure with the risk of a CV event. Results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs) compared to the “normal” group or to the lowest quartile of pulse pressure. The basic models were adjusted for age and sex. The larger models were further adjusted for BMI, physical working capacity (METs), self reported blood glucose and cholesterol, current smoking, resting brachial systolic blood pressure, and early parental history of cardiovascular disease. The statistical analyses were carried out with R (Version 2.11.1).

3. Results

Baseline characteristics of the study participants are outlined in Table 1, stratified by the CV event. A total of 170 subjects developed a CV event (30 TIAs, 109 nonfatal strokes and 31 fatal strokes) during the follow-up. The patients with a CV event were older and the blood pressures were higher. In patients without a CV event almost all other risk factors were more favorable compared with the CV event group.

Figure 2 shows Kaplan-Meier curves for CV event in different blood pressure groups. The curves diverge continuously and significantly ($P = .001$, log rank test) throughout the 16 years of follow-up.

The patients with elevated ankle blood pressure with or without exaggerated exercise blood pressure had 2.6–2.7-fold risk of a CV event compared with the reference group in the age- and gender-adjusted model (Table 2). In the wider model the hazard ratio was 2.2–2.4. In patients with obstructive changes in leg arteries (Group 4) the risk of a future CV event was 2.7-fold in the basic model and 2.4-fold in the multivariate adjusted model. The greatest hazard ratio (7.8 in the basic model and 5.8 in the wider model) was found in the unclassifiable patients (Group 5). In this group, 55 patients had ABI < 1.0 , and 25 patients had ABI < 0.9 .

Pulse pressures in the five blood pressure groups were 42.7 ± 11 , 54.4 ± 15 , 58.5 ± 14 , 49.0 ± 14 , and 52.6 ± 16 mmHg, respectively. Correlation between the pulse pressure and the ankle blood pressure in the blood pressure groups I–III was high ($r^2 = 0.48$). The correlation was lost, however, when obstructive changes were observed in the conduit vessels (Group 4) ($r^2 = 0.11$). The risk of a CV event by quartile of pulse pressure is shown in Table 3. The reference category is the lowest quartile of the pulse pressure. Significantly elevated risk for a CV event was found only for the fourth quartile in the smaller model.

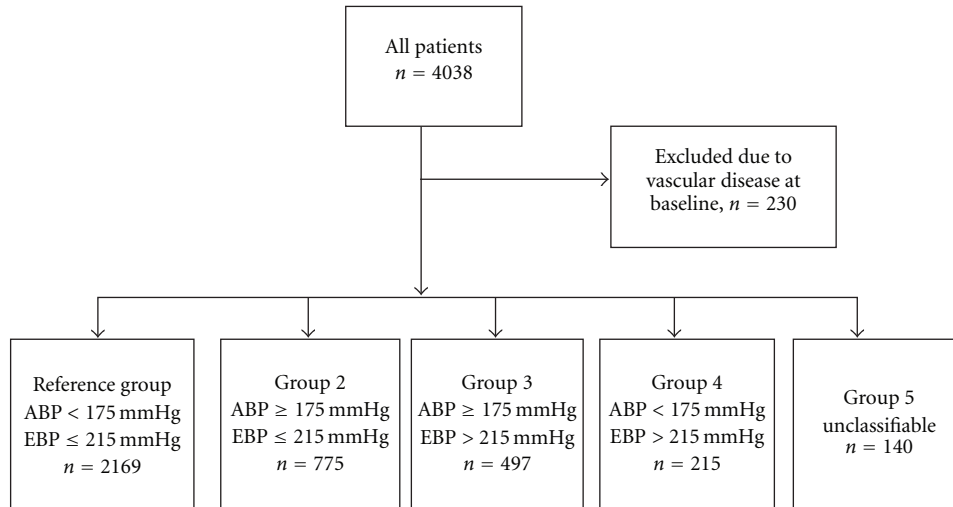


FIGURE 1: A flow-chart describing derivation of the blood pressure groups from all consecutive patients undergoing a clinical exercise test during the period 1989 to 1995. ABP: ankle blood pressure, EBP: brachial exercise blood pressure at the level of 150 Watts for men and 80 Watts for women.

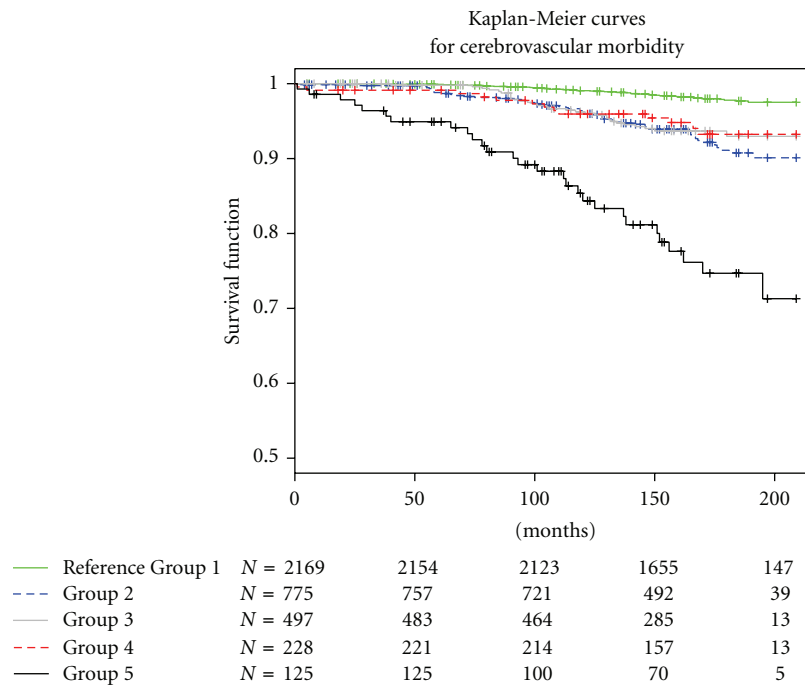


FIGURE 2: Kaplan-Meier curves for cerebrovascular (CV) events according to specified blood pressure group. Log-rank test for the difference between the blood pressure groups: $P < .0001$. The numbers indicate people remaining in the follow-up at different points in time. The reference group consists of patients with normal brachial pressure (<140 mmHg), ankle blood pressure <175 mmHg and exercise blood pressure ≤ 215 mmHg at the moderate exercise level. Group 2 had elevated ankle blood pressure (≥ 175 mmHg), but normal exercise blood pressure. Group 3 had elevated ankle and exercise blood pressure. Group 4 had ankle blood pressure <175 mmHg but elevated exercise blood pressure (discrepancy), and group 5 could not be classified because of poor exercise tolerance.

4. Discussion

The main finding of our study was that ABP, when considered together with EBP in a physiologically meaningful way, improved the prediction of incident CV events independently of classic risk factors. The healthy group with

normal ABP and EBP had the best prognosis, while the group with poor exercise tolerance had clearly the worst prognosis. For groups II–IV, the Kaplan-Meier curves were overlapping. Furthermore, ABP was a better predictor than the pulse pressure. Increased aortic and conduit vessel stiffness with high pressure pulsatility may be the explanation for our

TABLE 1: Baseline characteristics of participants with and without incident cerebrovascular event during the follow-up.

	No cerebrovascular event <i>n</i> = 3639	Cerebrovascular event <i>n</i> = 170	<i>p</i>
Age (years)	50 (10)	57 (10)	0.0001*
Men/women, <i>n</i> (%)	2423 (67)/1216 (33)	105 (62)/65 (38)	NS
Body mass index (kg/m ²)	26.1 (4)	26.6 (4)	NS
Syst. blood pressure (mmHg)	133 (18)	142 (19)	0.0001*
Diast. blood pressure (mmHg)	85 (11)	89 (10)	0.0001*
Pulse/min	74 (13)	74 (12)	NS
SBP80 (women)	181 (25)	193 (23)	0.001*
SBP150 (men)	201 (27)	212 (30)	0.0001*
SBP Max	203 (28)	205 (29)	NS
Ankle blood pressure (mmHg)	165 (27)	174 (34)	0.0001*
ABI	1.21 (0.2)	1.20 (0.2)	NS
Current smokers, <i>n</i> (%)	769 (22)	45 (29)	0.05 [†]
Self-reported abnormal total cholesterol, <i>n</i> (%)	1352 (37)	77 (45%)	0.001 [†]
Self-reported abnormal glucose, <i>n</i> (%)	273 (8)	20 (12)	0.04 [†]
Pos. family history, <i>n</i> (%)	1365 (38)	67 (39)	0.6
METs	7.8 (3)	6.4 (2)	0.0001*
Blood pressure groups			
Group I (reference)	2125 (58%)	44 (26%)	
Group II	719 (20%)	56 (33%)	
Group III	467 (13%)	30 (18%)	
Group IV	214 (6%)	14 (8%)	
Group V	114 (3%)	26 (15%)	0.0001 [†]

Data are mean (SD) or *n* and proportion (%), **t*-test, [†] χ^2 test.

SBP80: systolic blood pressure at the exercise level of 80 Watts.

SBP150: systolic blood pressure at the exercise level of 150 Watts.

SBPMax: maximum systolic blood pressure during exercise.

ABI: ankle brachial index.

METs: physical working capacity in metabolic equivalents.

Please see Section 2 for the explanation for the blood pressure groups.

TABLE 2: Hazard ratios (HR, 95% Confidence Interval (CI)) of cerebrovascular events according to the specified blood pressure groups (total *n* = 3808, no of events = 170).

Blood pressure group	Model 1			Model 2		
	HR	95% (CI)	<i>P</i> values	HR	95% CI	<i>P</i> values
Group I	1	(Reference)		1	(Reference)	
Group II	2.69	1.78–4.07	<.0001	2.24	1.43–3.52	<.0001
Group III	2.60	1.60–4.20	<.0001	2.09	1.21–3.61	.008
Group IV	2.71	1.44–5.10	.002	2.37	1.31–4.69	.007
Group V	7.82	4.67–13.12	<.0001	5.78	3.31–10.10	<.0001

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, BMI, resting brachial systolic blood pressure, smoking, early parental cardiovascular disease and physical working capacity (METs), self-reported elevated cholesterol, and abnormal blood glucose.

Please see Section 2 for the explanation for the blood pressure groups.

finding. The elevated ABP may be a useful surrogate marker for central and conduit arterial stiffness.

These findings extend our understanding of the behaviour and clinical significance of the ABP. In the recent PARTNER study [4], individuals with high ABI had much higher systolic blood pressure in the ankle and modestly lower brachial artery systolic blood pressure compared with those with normal ABI. The pathophysiologic conditions

causing stiffer arteries or stiffer surrounding tissues are insufficiently understood. While diabetes and degenerative vascular changes explain the phenomenon only in part [6], the increased stiffness, central and peripheral, could partly explain the elevated ABP. Aortic wall stiffness increases throughout the normal human lifespan, particularly in the presence of cardiovascular disease risk factors, and is first seen in increasing pulse wave velocity and central wave

TABLE 3: Hazard ratios (HR, 95% Confidence Interval (CI)) of cerebrovascular events by quartile of pulse pressure.

	Model 1			Model 2		
	HR	95% CI	P values	HR	95% CI	P values
Quartile I	1	(Reference)		1	(Reference)	
Quartile II	0.91	0.54–1.53	.7	0.92	0.55–1.56	.7
Quartile III	1.28	0.80–2.07	.3	1.21	0.75–1.95	.4
Quartile IV	1.62	1.04–2.65	.03	1.47	0.95–2.33	.08

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, BMI, smoking, early parental cardiovascular disease and physical working capacity (METs), self-reported elevated cholesterol, and abnormal blood glucose.

reflection (augmentation) [16, 27–29]. The stiffening of the aorta with minimal stiffening in the large peripheral muscular arteries decreases the normal impedance mismatch between the central and peripheral arteries enabling the transfer of excessive pulsatile energy into the periphery [17, 27]. Further research is needed to unravel the relationship of ABP to the pulse wave velocity which is a standard measure of the central aortic stiffness.

When the conduit vessels are free of flow limiting atherosclerotic stenoses, the main determinants of ABP are systolic blood pressure, enhanced pulse pressure, and local changes caused by rigidity of the arteries in the lower extremities. In these conditions, we can draw epidemiologic conclusions from ABP per se without indexing it to the brachial systolic pressure. The discrepancy between the ABP and exercise blood pressure may disclose those patients among whom stenotic changes along the conduit vessels decrease the ABP.

The good correlation between PP and ABP is lost when the stenotic changes limit the flow in the conduit vessels. The PP as a crude index of central arterial stiffness is not only hampered by age and heart rate but also by flow limiting atherosclerotic changes in the conduit vessels. That may explain why the peripheral PP is differently related to the risk of CV events in the literature [14–16, 19, 20, 23–26, 30] and why the peripheral PP has predictive value for ischaemic stroke also in normotensive patients [19, 31] among whom the flow limiting atherosclerotic changes are minor.

A strength of our study is the large sample size and the long follow-up period of 16 years. Also, in Finland the record linkage to the National Hospital Discharge Register and the National Causes of Death Register has good accuracy and coverage [32]. Some limitations should be acknowledged, however. The persons studied do not represent a random sample of the general population. The study participants are better educated and have a higher than average socioeconomic position. The ABP was measured from one leg only. The blood glucose and total cholesterol were self-reported and only half of the persons knew their glucose value. The persons without a known abnormal cholesterol or glucose values were taken as normal. The study was also limited by the lack of stroke subtyping. However, as shown by the ICD codes listed in Section 2, we excluded subarachnoid hemorrhages and included only intracerebral hemorrhages and ischemic strokes to keep our material more

homogenous. Furthermore, since ischemic strokes generally account for approximately 75%–80% of all strokes, the overwhelming majority of included strokes were of ischemic origin.

In conclusion, our results suggest new ideas about surrogate markers of subclinical vascular damage. The elevated ABP reveals better than PP the early adverse vascular changes, and the discrepancy between ABP and EBP discloses those patients in whom the atherosclerotic changes have propagated to the arterial lumen causing flow limiting stenosis. The ABP measurement may help us to better identify the patients who have the greatest risk for a CV event.

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Ankle blood pressure and dementia: a prospective follow-up study

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Background and objective Ankle blood pressure may be a useful indicator of arterial stiffness. The main aim of the present study was to examine the relationship of ankle blood pressure measured in midlife with the risk of dementia with advancing age. A secondary aim was to examine the relationship of physical exercise capacity in midlife with the risk of dementia.

Materials and methods This prospective follow-up study was carried out on individuals (mean age 50 years, 66% men) referred to a symptom-limited exercise test between August 1989 and December 1995. The cohort of 3859 individuals free of dementia and vascular disease at baseline was followed for 18 years. The significance of ankle blood pressure as a predictor of incident dementia was analyzed using Cox proportional hazard models, controlling for several confounders including brachial systolic blood pressure.

Results Clinically incident dementia was observed in 123 of the 3859 participants during the mean follow-up period of 18 years. Significant associations were found between the elevated ankle blood pressure at baseline and clinically incident dementia during the follow-up. In individuals with normal resting and exercise brachial

blood pressure but elevated ankle blood pressure, the hazard ratio was 1.58 (95% confidence interval 1.04–2.40, $P=0.03$, adjusted for age and sex). However, cardiovascular fitness, measured as metabolic equivalents at baseline, was inversely associated with dementia.

Conclusion These results suggest that ankle blood pressure has an independent value as a marker of arterial stiffness or subclinical atherosclerosis and a risk of future dementia. *Blood Press Monit* 18:16–20 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Vascular factors play a major role in the etiology and pathogenesis of brain degeneration. Especially, pre-existing cerebrovascular and cardiovascular diseases are strongly linked to vascular cognitive impairment (VCI) and late-onset dementia. The integrity of the vasculature is therefore essential for the optimal functioning of the brain. It is increasingly being recognized that cardiovascular risk factors also predispose to dementia and accelerate its progression [1–5]. Vascular and neurodegenerative pathologies are additive in influencing the clinical presentation of dementia.

The evidence for single clinically defined cardiovascular risk factors associated with incident dementia is, however, inconsistent when the life-course perspective is considered. Hypertension during midlife may increase the risk of dementia [6–8], but no convincing evidence exists that lowering blood pressure in late life prevents the development of VCI or dementia in hypertensive patients with no apparent previous cerebrovascular disease [9–12]. The association with hypercholesterolemia and dementia is even less robust, after taking age and competing mortality into account [3,10], although in most studies,

the high midlife cholesterol and other lipids play a role in increasing the risk [4,5], but the course of the converging pathway is debated [1,9]. In the elderly, diabetes is perhaps the most consistent predictor of cognitive decline [2,8,13]. Diabetes and metabolic syndrome increase the risk of dementia by 2–2.5-fold, particularly vascular dementia and especially in APOE e4 carriers [2]. As the incidence of VCI or dementia is strongly dependent on age, reducing mortality by preventing cardiovascular diseases could lead to an actual increase in the absolute number of VCI or dementia cases. Although a large group of individuals will develop VCI or dementia without a burden of vascular risk factors earlier in life, new screening tools to detect patients at risk are essential.

In recent years, artery stiffness and central aortic pressure have gained importance as useful indicators of the general condition of the circulatory system. Elevated arterial stiffness is a result of structural and functional changes in the vessel wall that occur with aging and is associated with higher systolic blood pressure and pulse pressure, elevated pulse wave velocity (PWV), and atherosclerosis. In a cross-sectional analysis of the Maine-Syracuse Longitudinal Study, PWV interacted with age in a

multiplicative manner to impair cognitive performance [14]. In the Rotterdam study, however, PWV was not associated with cognitive decline over time [15]. The negative longitudinal finding may be explained by regression to the mean and selection bias through participant attrition [14,15]. In any case, arterial stiffness becomes more prevalent with advancing age and because increasing numbers of adults are surviving into old age, arterial stiffness as a risk factor has received more attention.

The aim of our study was to evaluate the association between the ankle blood pressure (ankle-BP) and clinically incident dementia in a large prospective follow-up study. As proposed earlier by us [16,17] and others [18,19], elevated ankle-BP is a sensitive surrogate marker of arterial stiffness and central blood pressure. In our previous studies, we found that the elevated ankle-BP provided an added value over and above the traditional cardiovascular risk factors in the prediction of cardiovascular disease and stroke [16,17,20]. Now, our working hypothesis was that the elevated ankle-BP might be a significant predictor of clinically incident dementia and the prediction might be independent of the usual brachial blood pressure. In addition, we examined whether the physical exercise capacity in midlife predicts dementia in advanced age.

Materials and methods

Cohort

The prospective follow-up study was initiated in August 1989. The methods of baseline data collection have been described in our previous paper [17]. In brief, the patients were referred by occupational health physicians to a symptom-limited exercise test to rule out coronary heart disease and evaluate physical fitness. All patients were interviewed and information on demographics, cholesterol, blood glucose, family history, and medical history was collected. Patients with a history of cardiovascular disease at baseline were excluded from the analyses. The final study cohort included 3859 patients from the group of 4038 consecutive ambulatory patients.

Measurements of blood pressure and construction of the blood pressure groups

Ankle and brachial blood pressures were obtained simultaneously after a 5-min rest in the supine position. Brachial blood pressure was measured using a standard mercury sphygmomanometer. Ankle-BP was measured from the right leg using a Doppler probe with a mercury sphygmomanometer. Thereafter, a stepwise symptom-limited bicycle exercise test was continued until the patient refused to continue or until the attending physician felt it unsafe to continue. Exercise blood pressure at the moderate exercise level (150W for men and 80W for women) was used in the analysis. Initially, the patients were divided into five groups on the basis of ankle and exercise blood pressures [16,17,20], but for the present

dementia analyses, the groups were collapsed into four to ascertain a reasonable number of incident dementia cases for each group. The reference group included 'normal' patients with normal ankle-BP (< 175 mmHg) and normal systolic blood pressure (\leq 215 mmHg) at the moderate exercise level. Group 2 included patients with elevated ankle-BP (\geq 175 mmHg) but normal exercise blood pressure (\leq 215 mmHg). Group 3 had elevated exercise blood pressure with normal or elevated ankle-BP. Patients in group 4 were unclassifiable because they could not tolerate the moderate exercise level.

Follow-up

The follow-up was 18 years, until the end of 2008, using record linkage of the study data with the National Hospital Discharge Register, the National Causes of Death Register, the National Drug Reimbursement Register, and the National Pharmacy Register. ICD-9 codes 2900A, 3320A, 3321A and ICD-10 codes F001–F009 and F01–F03 were used for the diagnosis of dementia. In 46 cases, the diagnosis was made on the basis of chronic use of dementia medication. These were identified using the Anatomic Therapeutic Classification codes N06DA02–N06DA04 and N06DX01 from the National Pharmacy Register containing all drugs prescribed by a doctor. The primary outcome was clinically incident dementia without subtyping.

Statistical methods

Dichotomous variables were compared using χ^2 -tests and continuous variables using *t*-tests. Cox proportional hazards regression analysis was used to estimate factors associated with time to incident dementia. Models were adjusted for age, sex, smoking, physical working capacity, self-reported elevated cholesterol and abnormal blood glucose, early parental cardiovascular disease, and resting brachial systolic blood pressure. Person-years of follow-up were calculated from the patients' examination date. The outcome date was the date on which dementia was diagnosed and the censoring date was either the date of death from another cause or 31 December 2008. We carried out a sensitivity analysis by excluding those dementia cases where the diagnosis was made only on the basis of medication use, but the results remained consistent with the original findings. Therefore, the results obtained using the entire material are reported. Statistical analyses were carried out using R (Version 2.12.1; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Over the 18-year follow-up (60 266 person-years), 123 of the 3859 (3%) patients developed clinically incident dementia, including 44 with a new cardiovascular or cerebrovascular event. Altogether, 592 patients had a vascular event (15%). The clinical characteristics of the

study population are shown in Table 1, stratified by incident dementia. Patients with incident dementia were older than those without dementia and the majority of them were women. The resting brachial systolic and ankle-BP were higher in patients who developed dementia than in those who remained free of dementia, but there were not significant differences in diastolic blood pressure, BMI, or in self-reported cholesterol and blood glucose between the groups. The physical working capacity was better and pack-years of smoking were higher in patients who remained free of dementia than in the patients who developed dementia. The distribution of participants to the four blood pressure groups differed significantly by the status of dementia. Moreover, anti-hypertensive medication was more common in patients with future dementia.

Fifty-two patients with dementia (44.7% of the total 123) died during the follow-up, 15 because of a cardiac event and 14 because of a cerebrovascular event. Of the patients with dementia who survived, 14 had a cardiac event and six had stroke.

In the four blood pressure groups, dementia was observed in 43 (2%) patients in group 1, 49 (6%) in group 2, 14 (2%) in group 3, and 17 (13%) in group 4. However, a cardiovascular or cerebrovascular event was diagnosed in 195 (8.8%) patients in group 1, 158 (20.3%) in group 2,

172 (23.3%) in group 3, and 67 (50.7%) in group 4, respectively. In the unclassifiable group, there were 17 patients with incident dementia; nine of these died during the follow-up, seven because of vascular causes. Four out of the eight patients who survived had a nonfatal vascular event. Abnormal ankle brachial index (< 0.9) at baseline was measured in eight patients. Almost half (47%) of this unclassifiable group died of cardiovascular or cerebrovascular causes during the follow-up period.

Figure 1 shows the Kaplan–Meier curves for clinically incident dementia in different groups. In groups 2 and 4, the curves diverged continuously and significantly ($P > 0.001$, log-rank test) throughout the 18 years of follow-up. The patients with elevated ankle-BP without exaggerated exercise blood pressure had a 1.58-fold risk of dementia compared with the reference group in the age-adjusted and sex-adjusted model and the hazard ratio was 1.59 in the wider model (Table 2). The observed hazard ratios were independent of resting brachial systolic blood pressure and several other potential confounders. In group 3, the statistical analysis is uncertain because of the small number of patients with dementia (14 patients).

For comparison, we calculated the hazard ratio for the brachial systolic blood pressure. In both models, we could not find any association between the systolic brachial blood pressure and dementia (Table 3). Only low cardiovascular fitness was associated with dementia ($P = 0.01$). The results did not alter considerably when the brachial systolic blood pressure was replaced with pulse pressure: In model 1, the hazard ratio (95% confidence interval) was 1.0 (0.99–1.01) ($P = 0.89$).

Table 1 Characteristics of participants who developed incident dementia during the follow-up and those who remained free of dementia

	Dementia (n=123)	No dementia (n=3736)	P-value
Age (years)	63.7 (7.7)	49.9 (9.6)	$< 0.0001^*$
Men/women [n (%)]	46/77 (63%)	2515/1221 (33%)	$< 0.0001^*$
Systolic BP (mmHg)	138 (20)	135 (20)	0.002*
Diastolic BP (mmHg)	85 (9)	85 (11)	0.7*
Pulse/beats (min)	72 (13)	74 (13)	0.05*
SBP80 (women)	188 (24)	182 (25)	0.06*
SBP150 (men)	205 (24)	201 (27)	0.35*
Ankle-BP (mmHg)	173 (31)	165 (27)	0.01*
ABI-index	1.21 (0.4)	1.20 (0.3)	0.72*
Smoking (years)	7.5 (12)	9.7 (12.5)	0.04*
BMI (kg/m ²)	26.1 (3.9)	26.1 (3.8)	0.92*
Self-reported abnormal total cholesterol [n (%)]	48/75 (39%)	1405/2329 (38%)	0.83†
Self-reported abnormal glucose [n (%)]	12/111 (10%)	278/3455 (7%)	0.43†
Antihypertensive medication, yes, no (%)	46/77 (37%)	623/3113 (17%)	$< 0.0001^*$
METs	5.6 (1.8)	7.8 (2.8)	$< 0.0001^*$
Blood pressure groups			
Group 1 (reference)	43 (35%)	2170 (58%)	
Group 2	49 (40%)	729 (20%)	
Group 3	14 (11%)	722 (19%)	
Group 4	17 (14%)	115 (3%)	0.0001†

Please see the Materials and methods section for the explanation for blood pressure groups. Data are mean (SD) or N (%).

ABI, ankle brachial index; BP, blood pressure; METs, physical working capacity in metabolic equivalents; SBP80, systolic blood pressure at the exercise level of 80 W; SBP150, systolic blood pressure at the exercise level of 150 W.

* t-test.

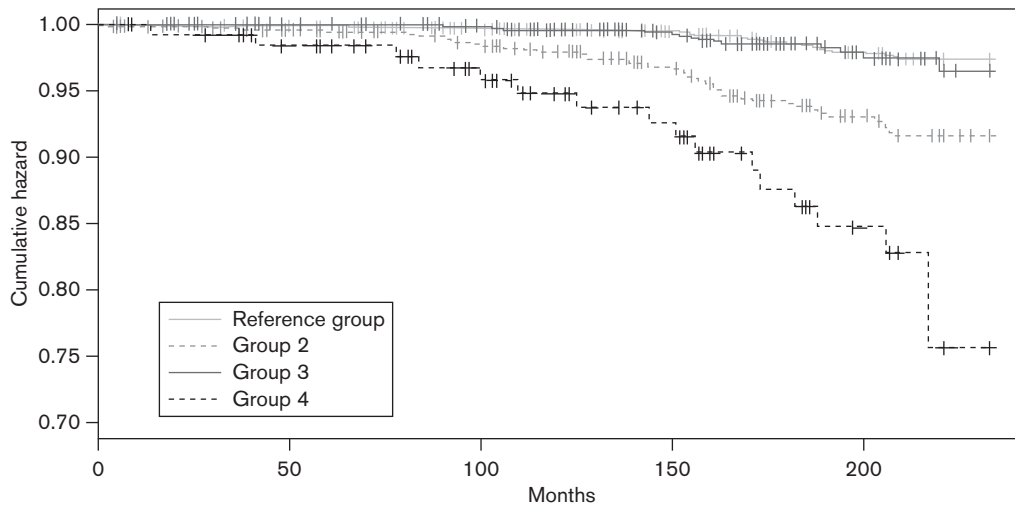
† χ^2 -test.

Discussion

Our present study indicates that elevated ankle-BP predicted clinically incident dementia during the follow-up of 18 years, independent of several other risk factors, including resting brachial blood pressure. The other important finding was the inverse association of physical exercise capacity in midlife with incident dementia, which has also been observed by others [21].

Elevated ankle-BP is a sensitive surrogate marker of arterial stiffness. In a cross-sectional study, elevated stiffness measured as PWV was found to be of additional value over the traditional cardiovascular risk factors in the prediction of poor cognitive function and dementia [22], but in prospective studies, the link has been unclear [15]. In our earlier work, we found that ankle-BP provides a significant added value over and above the traditional cardiovascular risk factors in predicting coronary heart disease and stroke events [16,17,20]. The present work extends these findings to dementia. The stiffening of the aorta with minimal stiffening in the large peripheral muscular arteries decreases the normal impedance mismatch between the central and the peripheral arteries, enabling the transfer of excessive pulsatile energy in the periphery,

Fig. 1



Kaplan–Meier curves for dementia.

Table 2 Hazard ratios (95% confidence interval) of dementia according to the specified blood pressure groups (total n=3859, number of dementia=123)

Blood pressure group	Model 1			Model 2		
	HR	95% CI	P-value	HR	95% CI	P-value
Group 1	1	Reference	–	1	Reference	–
Group 2	1.58	1.04–2.40	0.034	1.59	1.00–2.56	0.05
Group 3	0.82	0.44–1.52	0.53	0.9	0.45–1.77	0.74
Group 4	2.26	1.24–4.13	0.008	1.93	1.00–3.80	0.05

CI, confidence interval; HR, hazard ratio; METs, physical working capacity in metabolic equivalents; model 1, adjusted for age and sex; model 2, adjusted for age, sex, smoking, physical working capacity (METs), early parental cardiovascular disease, and resting brachial systolic blood pressure.

thus creating elevated ankle-BP. The brain is perfused at high-volume flow with very low vascular resistance. Despite good autoregulation, the increased arterial stiffness with augmented central pulse pressure exerts high-pressure fluctuation in the cerebral circulation. This may lead to remodeling of large and small vessels, causing endothelial dysfunction and oxidative stress with microvascular brain damage [23].

Elevated exercise blood pressure and normal or low ankle-BP enable the identification of those patients in whom atherosclerotic stenotic changes along the conduit vessels invalidate the evaluation of arterial stiffness using ankle-BP measurement. This group had a high risk for cardiovascular and cerebrovascular diseases in our pre-

Table 3 Cox proportional hazards ratios, dependent variable: dementia

	β	Hazard ratio	P-value	95% confidence interval
Age (years)	0.15	1.16	<0.001	1.13–1.19
Sex	0.38	1.46	0.1	0.92–2.32
Systolic BP (mmHg)	–0.002	0.98	0.67	0.99–1.03
BMI (kg/m ²)	–0.017	0.98	0.51	0.93–1.03
METs	–0.179	0.84	0.01	0.73–0.96
Current smoking	–0.004	1.00	0.64	0.98–1.01
Pos. family history	0.197	1.22	0.31	0.83–1.78

METs, physical working capacity in metabolic equivalents; Pos. family history, early parental cardiovascular disease.

vious studies [17,20], but the lack of an association with dementia is surprising. Many potential sources of bias were identified: the small number of patients with dementia in the study group, the large number of patients censored because of the cardiovascular events, and last but not least, the measurement itself. According to the literature, the impact of midlife risk factors on VCI or dementia is mediated more through arterial stiffness caused by hypertension than stenotic changes caused by high cholesterol [2,3,8,10,24].

Two other important aspects have to be mentioned. First, the population under study is relatively young and the follow-up is short to find an effect on incident dementia. As a consequence, the number of participants with incident dementia was low. Second, the majority of our dementia patients were women, although 66% of our

study group were men. It is likely that men had died because of other vascular pathologies before reaching the age where dementia starts to become manifest. This is supported by the fact that 42% of the patients with dementia died during the follow-up and the vascular events were common in individuals with dementia. The relative risk of dementia because of cardiovascular disease is attenuated over time as a consequence of the impact of cardiovascular disease on mortality [2,3,10,14,15].

The strengths of our study are the long follow-up time, the large sample size, and the prospective design. There are also some limitations. Our patients did not undergo neuropsychological examinations and we therefore focused only on cognitive decline severe enough to be clinically detected as dementia without any subtyping. It has been shown, however, that the specificity of dementia coding was good in the Swedish healthcare register and the Finnish register system is very similar to the Swedish one in this respect [25]. The patients studied were better educated and had higher than average socioeconomic positions. Thus, they do not represent a random sample of the general population. The blood glucose and total cholesterol were self-reported and only half the patients knew their glucose value.

Conclusion

The addition of ankle-BP measurement to the conventional upper limb blood pressure measurement and assessment of the physical exercise capacity may improve our ability to assess the risk of a future vascular event and also dementia. Effective modification of risk factors before the development of irreversible changes is essential, as the neurodegenerative process underlying dementia is initiated decades before the clinical symptoms appear. Elevated ankle-BP may help to identify the patients who are at risk of a vascular event and later dementia.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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