Riitta-Liisa Vasunta

AMBULATORY BLOOD PRESSURE

ASSOCIATION WITH METABOLIC RISK INDICATORS, RENAL FUNCTION AND CAROTID ARTERY ATHEROSCLEROSIS
RIITTA-LIISA VASUNTA

AMBULATORY BLOOD PRESSURE
Association with metabolic risk indicators, renal function and carotid artery atherosclerosis

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 7 of Oulu University Hospital, on 30 November 2012, at 12 noon

UNIVERSITY OF OULU, OULU 2012
Blood pressure is usually measured on a clinic visit as a momentary value. It can also be defined as a continuum based on several repeated measurements. Ambulatory blood pressure measurement (ABPM) is a method of repeated BP measurements targeted to evaluate the circadian blood pressure (BP). Nondipping, i.e., the lack of reduction of BP during the night, has been shown to associate with cardiovascular endpoints. The aim of this study was to investigate the association between 24-hour ABPM and cardio-metabolic confounders in a cross-sectional, population-based study design. Particular attention was paid to the nondipping phenomenon.

Adiponectin, a hormone secreted by the adipose tissue, has vasoprotective and anti-inflammatory effects. Reduced adiponectin level has been associated with hypertension. In this study adiponectin level was inversely associated with daytime systolic BP, but showed no association with nondipping.

Hypertension is one component of metabolic syndrome (MS). MS has been associated with nondipping. The association between ABPM and metabolic abnormalities was studied in subjects without known hypertension or type 2 diabetes. Subjects with impaired glucose metabolism were more likely to belong to the group of nondippers.

Fatty liver is considered as the hepatic manifestation of MS. A significantly higher prevalence of fatty liver has been seen in hypertensives compared to normotensive controls, elevating their risk for cardiovascular morbidity. The association between ABPM characteristics and fatty liver was evaluated in the present study. Significantly higher systolic ABPM levels were seen in subjects with fatty liver, but no association with nondipping existed.

The kidney vasculature is prone to injury under a high continuous circadian BP load and lacking nighttime drop. This may lead to diminished glomerular filtration rate. Our study showed a significant independent association between renal function and the dipping status. Reduction in renal function was associated with increased risk of nondipping pattern.

Carotid intima-media thickness (cIMT), the surrogate marker of early atherosclerosis, has been associated with blunted nocturnal BP drop. The association between cIMT and dipping status was explored. Nondipping pattern was associated with increased cIMT.

In conclusion, ABPM specifies the information of circadian and nighttime BP level not achievable with conventional BP measurement. This is especially beneficial in metabolic abnormalities when the risk of cardiovascular morbidity is increased.

**Keywords:** adiponectin, ambulatory blood pressure, atherosclerosis, dipping pattern, fatty liver, metabolic syndrome, renal insufficiency
Vasunta, Riitta-Liisa, Ambulatorinen verenpaine. Yhteys metabolisiin riskitekijöihin, munuaistointiin ja kaulavaltimoseinänpäin ateroskleroosiin

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta, Kliinisen lääketieteen laitos, Sisätaudit; Biocenter Oulu; Kliinisen tutkimuksen keskus, Oulun yliopiston sairaala, PL 5000, 90014 Oulun yliopisto


Oulu

Tiivistelmä


Väitöstutkimuksessa vuorokausiverenpaineen mittattuihin käyttämällä ambulatorisella verenpaineennittauksella. Lisäksi verenpainetason mitattuihin tavallisesti tapaukseen vastaanottokäynnin yhteydessä. Maksan rasvaisuutta ja kaulavaltimoseinän paksuuttua tutkittiin ultrahyvin laitteella. Tavanomaisten taustamuuttujien lisäksi kerättiin laboratoriotietoja sokeriaineenvaihdunnasta, munuaissuodoksen määrästä sekä rasvakuudoksen erittäimän adiponektiinhormonin määrästä.


Asiasanat: adiponektiini, ambulatorinen verenpaine, ateroskleroosi, dipping-ilmiö, metabolinen oireyhtymä, munuaisten vajaatoiminta, rasvamaksas
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## Abbreviations

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ABP</td>
<td>ambulatory blood pressure</td>
</tr>
<tr>
<td>ABPM</td>
<td>ambulatory blood pressure monitoring</td>
</tr>
<tr>
<td>BIF</td>
<td>carotid artery bifurcation</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>Bpm</td>
<td>beats per minute</td>
</tr>
<tr>
<td>CCA</td>
<td>common carotid artery</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>CT</td>
<td>computer tomography</td>
</tr>
<tr>
<td>CV</td>
<td>cardiovascular</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>HDL</td>
<td>high-density lipoprotein</td>
</tr>
<tr>
<td>ICA</td>
<td>internal carotid artery</td>
</tr>
<tr>
<td>cIMT</td>
<td>carotid intima-media thickness</td>
</tr>
<tr>
<td>LDL</td>
<td>low-density lipoprotein</td>
</tr>
<tr>
<td>MS</td>
<td>metabolic syndrome</td>
</tr>
<tr>
<td>NAFLD</td>
<td>non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>OGTT</td>
<td>a two-hour oral glucose tolerance test</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>T2D</td>
<td>type 2 diabetes</td>
</tr>
<tr>
<td>TG</td>
<td>triglycerides</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
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List of original publications

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1 Introduction

Hypertension is a common health problem concerning a large proportion of population and a leading global risk factor for the burden of cardiovascular disease. (Catala-Lopez et al. 2011) High BP is often combined with metabolic disorders and diabetes. (Alistar & Datcu 2010, Chimonas et al. 2010, Fogari et al. 2010, Pierdomenico & Cuccurullo 2010, Safar et al. 2011) Although hypertension is the most prevalent treatable vascular risk factor it is poorly understood how it causes end-organ damage and vascular events. (Rothwell 2010) Diagnosis and follow-up of high BP relies mostly on office BP measurements targeting to estimate the true usual BP level. However, the within-individual standard deviation of office SBP at different clinic visits has been 10 to 20 mm Hg. (Hebel et al. 1980)

Several artifacts can affect office BP measurements. Environmental factors such as doctor’s office, physiological and emotional state of the patient and other confounding factors may interfere with achieving the true BP level. Home measurements are used to minimize the erroneous values, but they are not useful for examining nighttime BP and BP drop during sleep.

Normotensive subjects usually have a clear circadian rhythm characterized by higher pressures at daytime and lower at nighttime. The circadian profile consists of a nighttime drop called dipping and an early morning surge. The dipping pattern was described for the first time at in 1988 by O’Brien et al. (O’Brien et al. 1988) The association between lacking dipping phenomenon (i.e. nondipping) and unfavorable CV outcome has been widely reported (Bianchi et al. 1994, Cuspidi et al. 2004a, O’Brien et al. 1988, Ohkubo et al. 2002, Shimada et al. 1992, Staessen et al. 1999, Verdecchia et al. 1990, Verdecchia et al. 1994, Verdecchia 2000), although there are some studies which could not verify such an association. (Björklund et al. 2004, Kario et al. 2001a) Numerous studies have shown the association between nondipping pattern and diabetes. (Cuspidi et al. 2010, Sturrock et al. 2000)

ABPM is a method of repeated BP measurements enabling the evaluation of the circadian BP profile during normal daily life and during sleep, contrary to conventional BP measurement. ABPM provides more accurate and specific BP assessment in patients with suspected or documented hypertension. (Hansen et al. 2011, Sorof et al. 2000) The superiority of ABPM to clinic measurement in predicting CV mortality and outcome has been considered (Björklund et al. 2004, Clement et al. 2003, Staessen et al. 1999) unrelated to office BP values (Conen &

Adiponectin is a hormone secreted by the adipose tissue. It has insulin-sensitizing, antiatherogenic, and anti-inflammatory properties. (Adachi & Brenner 2008) Low serum adiponectin level has been associated with body adiposity and increased weight. (Hara et al. 2006, Li et al. 2011) Hypoadiponectinemia has been suggested to be involved in the pathogenesis of hypertension. (Chow et al. 2007) Kubota et al. (2002) demonstrated in an animal model of adiponectin knockout mice that neointimal thickening and increased proliferation of vascular smooth muscle cells was seen in injured arteries. They suggested that adiponectin plays a protective role against insulin resistance and atherosclerosis in vivo. (Kubota et al. 2002) Hypoadiponectinemia has been shown to be a risk factor for hypertension independent of insulin resistance and diabetes. (Iwashima et al. 2004). Low levels of adiponectin have been revealed to associate with left ventricular hypertrophy, a common hypertension-related complication, even after adjustment for the commonly recognized risk factors. (Pääkkö et al. 2010)

High BP in association with obesity exposes to impaired elasticity in large and small arteries in apparently healthy middle-aged and older adults (Fjeldstad et al. 2007). The association between impaired metabolic state, decreased artery wall elasticity and impaired pulse wave velocity has been previously documented. (Cameron et al. 2003, Jennings & Kingwell 2004, Kool et al. 1995, Prisant et al. 2006, Salomaa et al. 1995)

The metabolic syndrome (MS) is a cluster of cardio-vascular risk factors that increase the risk of CV morbidity and mortality. (Alberti et al. 2005, Isomaa et al. 2001, Lakka et al. 2002, Reynolds & He 2005) According to the definition of the International Diabetes Federation (Alberti et al. 2005) MS is a state characterized by central obesity in association with two of the following factors: raised fasting plasma glucose, raised triglycerides, reduced HDL cholesterol and high BP. High BP in concert with impaired glucose metabolism, thrombogenic state, subclinical inflammation, renal impairment and unfavorable lipid profile remarkably increases the risk of CVD.

Non-alcoholic fatty liver disease is a condition in which fat is accumulated in the liver of a subject who does not drink much or any alcohol. It has widely been suggested that non-alcoholic fatty liver disease (NAFLD) is the hepatic
manifestation of the metabolic syndrome. (Bugianesi et al. 2005, Dowman et al. 2011, Marchesini et al. 2001)

CVD has been shown to be the most important cause of morbidity and mortality among patients with chronic renal insufficiency. (Foley et al. 2010) A significant interaction between SBP and kidney function status and pulse pressure and CKD status has been noted. (Kendrick et al. 2010) Hypertension is the most important factor leading to nephropathy. Thus early detection of high BP is essential among diabetic subjects (Agarwal et al. 2011). High BP and poorly controlled hypertension precipitates the progression of impaired renal function. On the other hand, a diminished SBP lower than 120 mmHg and increased pulse pressure have been associated with increased all-cause mortality among subjects with renal failure. According to Berl et al. (2005) BP ≤ 120/85 may be associated with an increase in CV events in patients with diabetic nephropathy although it may decrease the risk of stroke (Berl et al. 2005). Based on this, information of real BP level seems to have exceptional importance in renal failure.

Carotid artery thickening has been considered as an early stage of atherosclerosis. High BP has been shown to be one of the main risk factors for vascular injury. (Homer et al. 1991, Willeit & Kiechl 1993) Carotid wall examination by ultrasound is considered a reliable method to investigate the wall thickness and atherosclerotic plaques. (Bots et al. 1993, O'Leary et al. 1992)

The purpose of the present study is to investigate the possible association between unfavorable cardio-metabolic confounders and 24-hour BP measurements, in particular the dipping phenomenon.
2 Review of the literature

2.1 Office and out-of-office blood pressure

Defining the BP level by using mercury sphygmomanometer and stethoscope has been used since the end of the nineteenth century. Office BP measurement gives a momental, cross-sectional view of diurnal BP. However, BP is a continuum which for most people varies throughout the day and is affected by the physiological state and environmental circumstances. In addition, office BP is prone to interobserver and intraobserver bias. Lacking capacity to detect white-coat hypertension has also been noted. (O’Brien et al. 2001, O’Brien 2011) A great deal of factors can interfere with the measurement, e.g. talking while measuring, failure to allow a rest period before measurement, exposure to cold, cuff that is too small or too large, wrong position of patient’s arm in respect to heart level, deflating the cuff too rapidly and rounding the BP values by the measurer. (McAlister & Straus 2001) ABPM approximates the “true” BP level more accurately than office BP measurement and has therefore been proposed to be the reference standard for diagnosing hypertension. (Hodgkinson et al. 2011)

2.1.1 White coat BP and masked hypertension

White coat BP is defined as raised office BP measurement (BP ≥ 140/90 mmHg) in subjects whose daytime ABPM is lower than 135/85 mmHg. (Verdecchia et al. 2005) White coat hypertension was described for the first time by Mancia et al. (Mancia et al. 1983a) by measuring the intra-arterial BP of a hospitalized patient. When the doctor approached the bedside the BP of the patient immediately rose about 27 mmHg/15 mmHg (mean SBP/DBP), with the peak persisting for 1–4 minutes after arrival. Intraindividual variation was large (4–75 mmHg/1–36 mmHg) unrelated to age, sex or BP at baseline. Heart rate correlated only slightly with BP rise (average peak response about 16 bpm, range 4–75 bpm). The phenomenon of white coat BP elevation has also been verified in other studies (Owens et al. 1999) and it has been considered to be a rise in BP seen only when measured in medical care environment (White 2003).

By noninvasive ambulatory BP monitoring about 15–30% of patients who are hypertensive in the physician’s office seem to have normal BP outside the office. (Pickering et al. 1988, Pickering 1997, Staessen et al. 1993, Verdecchia et al. 1994)
Muxfeldt et al. investigated resistant hypertensives, among whom 37% were shown to be white-coat hypertensives. (Muxfeldt et al. 2005) White coat hypertension has been associated with increased arterial stiffness (de Simone et al. 2007), left ventricular hypertrophy (de Simone et al. 2007) and subclinical target organ damage (Cuspidi et al. 1995, Kario et al. 2001b) In the large population-based PAMELA study researchers pointed out the unfavorable composition of white coat hypertension and metabolic syndrome. (Sega et al. 2001) Aging may increase the susceptibility to white coat hypertension. (Dolan et al. 2004)

Masked hypertension (reverse white coat hypertension, isolated hypertension) is defined as normal office BP in combination with elevated home BP. Masked hypertension is seen in normotensive and hypertensive subjects. The reported prevalence has been 10–20%. (Kawabe et al. 2005, Pickering et al. 2002) An association between masked hypertension and target organ damage has been shown (Bjorklund et al. 2004, Liu et al. 1999, Lurbe et al. 2005, Ohkubo et al. 2005), and the importance of home BP measurements is reported to have a better predictive value compared with clinical BP measurements. (Bobrie et al. 2004)

2.1.2 Circadian profile of blood pressure

Normotensive subjects have a clear diurnal BP rhythm characterized by a BP decline during sleep and an early morning surge. This circadian BP variation has been verified sphygmomanometrically and by intra-arterial methods in sleep laboratories. (Dimsdale & Heeren 1998)

According to Mancia et al. BP variability has been assessed by calculation of the standard deviation of 24-hour BP, SBP, DBP and mean arterial pressure (Mancia & Grassi 2000a). 24-hour MAP varies about 10% among subjects although interindividual differences are large. SBP seems to vary more than DBP based on standard deviation. The variations may be as much as 50–60 mmHg over 24-hours. (Mancia et al. 1983b, Mancia et al. 1993, Omboni et al. 1998) BP variation is related to central autonomic drive mediated by baroreflex mechanisms, which is an essential determinant of diurnal BP variability. (Conway et al. 1984, Mancia et al. 1997a, Mancia et al. 1997b) Since baroreflex sensitivity increases during sleep whereas BP decreases, Vaile et al. investigated whether the possible difference exists in baroreflex sensitivity between dipper and nondipper untreated hypertensives. No difference was found. (Vaile et al. 1996) Grassi et al. examined baroreflex function and muscle sympathetic nerve activity. They confirmed previous findings that the sympathetic activity seen in hypertensives was not of
baroreflex origin and concluded that baroreflex activity is unlikely to be involved in the magnitude of nighttime BP drop in hypertensive subjects. (Grassi et al. 2008) Nami et al. evaluated the effect of aerobic exercise on 24-hour BP in non-treated hypertensive subjects. The duration of the exercise period was three months. 48-hour ABPM was performed before and after the exercise period. Circadian BP declined in dippers, but not in nondippers, who remained nondippers also after the exercise period. They concluded that nondipper status “masking” endogenous or exogenous factors might prevail over the adrenergic-vagal balance modulating the diurnal BP synchronization. (Nami et al. 2000)

Most cross-sectional studies indicate that aging increases SBP values, but DBP can even decrease after the age of 50 to 60. In the Ohasama study the age-dependent SBP increase in men from their 20s to their 80s was smaller (9 mmHg) in ABPM than that measured in clinic setting (26 mmHg). (Imai et al. 1993)

Veerman et al. studied healthy young subjects during a 24-hour ambulatory registration. At nighttime the decrease of mean arterial pressure was 9 mmHg, heart rate was 18 beats per minute lower and cardiac output, stroke volume and total peripheral resistance increased (29%, 7% and 22% respectively) compared to daytime. They concluded that the absence of physical activity during nighttime is involved in the genesis of CV circadian rhythm. (Veerman et al. 1995)

Baumgart et al. studied (Baumgart et al. 1989) the diurnal BP of shift-workers and found adaptation of 24-hour BP curve to shifted activity indicating that activity determines the diurnal BP profile. They concluded that BP is largely independent of internal circadian rhythm. According to Shea et al. there exists a robust endogenous circadian rhythm in BP that appears to be unrelated to circadian rhythms in cortisol, catecholamines, cardiac vagal modulation, heart rate, or urine flow. (Shea et al. 2011) As a whole, the endogenous circadian timing is a complex system including the suprachiasmatic nucleus that conducts the orchestra of peripheral tissues such as heart, vasculature, kidneys, adrenal cortex and adrenal medulla. This results in neural and endocrine effects secondarily influencing alertness and sleep. (Kalsbeek et al. 2006) According to Shea et al., although there are animal studies concerning circadian clocks that affect BP, ischemia, reperfusion tolerance and vascular remodeling, the mechanistic circadian studies of CV function in humans are sparse. (Shea et al. 2011)
2.1.3 24-hour BP and prognosis


Sturrock et al. studied the relevance of circadian BP variation to future morbidity and mortality in patients with diabetes and found that loss of circadian variation in BP was associated with an increased mortality rate, regardless of diabetes type. (Sturrock et al. 2000) Gupta et al. demonstrated that asymptomatic obese adults with abnormal circadian BP variability and endothelial function exhibit unfavorable cardiometabolic profiles. (Gupta et al. 2010) The prognostic value of a higher ambulatory SBP and DBP in treated hypertensives was seen in the study of Clement et al. as high ABPM values predicted CV events even after adjustments with classic risk factors, including office BP measurements. (Clement et al. 2003). Concerning the predictive differences between SBP and DBP there is evidence that systolic BP might have more predictive value than diastolic (Sega et al. 2005) although predictive value of diastolic BP has also been reported (Hansen et al. 2005). The systolic night-day ratio has in particular been suspected to predict all-cause mortality and CV events. (Boggia et al. 2007, Fagard 2009)

2.2 Ambulatory Blood Pressure Measurement (ABPM)

ABPM has been available for nearly 40 years. The measurement was initially intra-arterial and was developed to determine BP during physical activity, work, rest and sleep. From the early 1980s noninvasive, fully automated methods became available. (O’Brien 2011, White 2003) ABPM is a method in which repeated BP readings take place while the patient undergoes normal daily activities. As normotensive subjects may have occasional high office values, ABPM is targeted to detect 24-hour BP profile for diagnosing hypertension. Recommendations suggest performing ABPM if white coat hypertension is suspected and before starting antihypertensive drugs, often as a lifelong treatment. (O’Brien et al. 2000, O’Brien et al. 2001, O’Brien 2011, Pickering et al. 2006) Moreover, ABPM has an important role in tailoring the treatment for better outcome in hypertensive patients. (Head et al. 2010) Symptoms suggesting hypotensive episodes can also be investigated with ABPM (World Health Organization-International Society of Hypertension Guidelines for the
management of hypertension. Guidelines subcommittee 1999). Table 1 summarizes the accuracy of different BP measuring methods. In addition, ABPM has been observed to help in rational drug prescribing and reducing misdiagnosis, and the cost effectiveness of ABPM was also shown in a recent study of Lovibond et al. (2011).

Table 1. Accuracy of different measuring methods in BP components.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ABPM</th>
<th>In-office BP</th>
<th>Home BPM</th>
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<tr>
<td>True*, mean BP</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Diurnal BP</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dipping</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BP variability</td>
<td>+</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Duration of drug effects</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Modified from Pickering et al. 2006. **“An estimate of the true” from Pickering**

According to O’Brien et al. (2001) ABPM measurements should consist of >14 SBP and DBP measurements by day and >7 measurements by night. ABPM values for defining normal BP and elevated BP differ from in-office borderlines. Based on firm evidence from a number of studies the recommended ABPM mean is ≤135/85 at daytime, ≤120/70–75 at nighttime and ≤130/80 during 24-hour period. (O’Brien et al. 2001, Head et al. 2010) Poor technique, unsuitable cuff, insufficient instructions to the patient, arrhythmias, small pulse volume and inability for the device to measure BP can cause failure in registrations. (O’Brien et al. 1993, O’Brien et al. 2000, O’Brien et al. 2001)

2.3 Dipping phenomenon

2.3.1 Definition of dipping

Dipping is considered as a categorical variable classifying the population according to day- and nighttime BP values. (Dimsdale & Heeren 1998) Individuals with nighttime BP elevation have also been registered. There is no clear standard time frame for separating “daytime” from “nighttime”, but most studies consider the period from 6 AM to 10 PM as daytime and from 10 PM to 6 AM as nighttime, while some researchers specify the awake-asleep periods using patient-reported diary to avoid misclassification. Some studies base dipping pattern on SBP (Bankir et al. 2008, Kario et al. 2000, Verdecchia et al. 2007, von
Kanel et al. 2004), some regard DBP values as more reliable because of their smaller variability (Mancia 2000a), and some use both SBP and DBP values (Ben-Dov et al. 2007, Cuspidi et al. 2006, Fallo et al. 2008, Grassi et al. 2008, Perk et al. 2001). Kaya et al. use either SBP or DBP (Kaya et al. 2010) while Hermida uses SBP and DBP separately (Hermida et al. 2008). Also mean arterial pressure (MAP) has been used (Fujii et al. 1999).

In a normal dipping pattern the reduction of BP during nighttime is ≥10% (dipper). In nondipping pattern the nighttime reduction compared to daytime BP is <10% (nondipper). Some subjects can be classified as extreme dippers (nocturnal fall of BP >20%) or inverse dippers or risers when the asleep BP is higher than the awake BP. (Fogari et al. 1993, Hamada et al. (Table 2)

![Image of Dipping phenomenon.](image)

**Table 2. Blood pressure and dipping pattern.**

<table>
<thead>
<tr>
<th>Dipping pattern</th>
<th>Daytime/nighttime BP difference (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>10–20%</td>
</tr>
<tr>
<td>Nondipping</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Extreme dipping</td>
<td>&gt;20%</td>
</tr>
<tr>
<td>Inverse dipping</td>
<td>&lt;0%</td>
</tr>
</tbody>
</table>

*[(Awake BP mean - asleep BP mean)/awake BP mean] x 100
2.3.2 Possible mechanisms of dipping

The exact mechanisms of nondipping are unknown and supposed to have multiple causes. The effects of physical activity, nocturnal urination (Perk et al. 2001), sleep quality (Carlson et al. 1993, Pedulla et al. 1995, Portaluppi et al. 1997), sodium intake and natriuresis (Fujii et al. 1999, Uzu et al. 1997), race (Chen et al. 1995, Harshfield et al. 2002, Hyman et al. 2000, Ohkubo et al. 2002) and sympathetic activity (Lombardi & Parati 2000, Sherwood et al. 2002) have been considered to affect the diurnal BP variation. It has been stated that β-adrenergic receptor sensitivity may contribute to relationships between blunted nocturnal BP dipping and various cardiovascular end points. (Profant et al. 2002) The effects of nighttime horizontal posture and medication administration time have been speculated. (Grassi et al. 2008, Imai et al. 1993, Mancia et al. 1993, van der Steen et al. 2000)

2.3.3 Dipping as a cardiovascular risk factor

Nondipping status has been related to risk factors. Cuspidi et al. detected an approximately three-fold higher prevalence of a persisting nondipping pattern in diabetic hypertensive patients as compared with non-diabetics. In diabetic subjects a single ABPM recording was even more reliable than in non-diabetics (Cuspidi et al. 2006) and thus has a more steady predictive value especially in diabetics.

Nondipping has been associated with hypertension and microalbuminuria. (Bianchi et al. 1994, Berrut et al. 1996, de la Sierra et al. 2009, Muxfeldt et al. 2003) The combination of nondipping and nephropathy has particularly been related to higher mortality rate, and the role of ABPM has been underlined in an effort to alter outcome in subjects with renal failure. (Sturrock et al. 2000)

Nondipping status has been noted as a sign of autonomic dysfunction even in the early stages of Parkinson’s disease when orthostatic hypotension is not present. (Sommer et al. 2011) Hereby, ABPM may also benefit patients with Parkinson’s disease.

The absence of nighttime BP drop has been associated with silent cerebrovascular damage in elderly subjects. Reverse dipping (rising) has been associated with the development of hypertensive cerebrovascular damage. (Kario et al. 1996, Kario et al. 2001a, Kario et al. 2001b, Shimada et al. 1992) On the other hand, cerebral hypoperfusion is a significant risk in the elderly and
treatment of hypertension should be administered with care and with regard to nocturnal BP. (Watanabe et al. 1996)

Nondipping pattern is considered as an important predictor of CV morbidity, mortality and target-organ damage. This has been demonstrated in population-based studies (Ingelsson et al. 2006, Ohkubo et al. 1997, Sherwood et al. 2001) and among hypertensives (de la Sierra et al. 2009, Dolan et al. 2005, Kario et al. 2001a, O'Brien et al. 1988, Staessen et al. 1999, Verdecchia et al. 1994). Fogari et al. stated that as the absence of nocturnal BP fall has been associated with the increased prevalence of left ventricular hypertrophy and atherosclerotic CVD, its detection by ABPM might be of prognostic and therapeutic importance. (Fogari et al. 1993) More studies considering the relation between nondipping and morbidity are presented in Table 3.
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>group</th>
<th>Age (SD)</th>
<th>Dipping definition</th>
<th>nondippers (%)</th>
<th>Nondipping associated with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agorasti et al. 2011</td>
<td>71**</td>
<td>hypertensive</td>
<td>33–81</td>
<td>SBP</td>
<td>52%</td>
<td>alterations in hemostasis</td>
</tr>
<tr>
<td>de la Sierra et al. 2009</td>
<td>42947*,**</td>
<td>hypertensive</td>
<td>53 (±13)</td>
<td>SBP</td>
<td>41%* 53%**</td>
<td>CV risk</td>
</tr>
<tr>
<td>Kaya et al. 2009</td>
<td>126*</td>
<td>hypertensive, controls (40)</td>
<td>51 (±4)</td>
<td>Either SBP or DBP</td>
<td>47%</td>
<td>increased platelet activity and inflammatory activity</td>
</tr>
<tr>
<td>Fallo et al. 2008</td>
<td>80**</td>
<td>hypertensive</td>
<td>49.7 (±9)</td>
<td>SBP+DBP</td>
<td>41%</td>
<td>liver steatosis, insulin resistance, low adiponectin</td>
</tr>
<tr>
<td>Hermida et al. 2008</td>
<td>250*</td>
<td>hypertensive</td>
<td>60 (±12)</td>
<td>SBP, DBP separately</td>
<td>86%, 43%</td>
<td>drug administration once a day</td>
</tr>
<tr>
<td>Grassi et al. 2008</td>
<td>79*</td>
<td>hypertensive</td>
<td>47 (±2)</td>
<td>SBP+DBP</td>
<td></td>
<td>sympathetic activity</td>
</tr>
<tr>
<td>Ben-Dov et al. 2007</td>
<td>4006**</td>
<td>hypertensive, normotensive</td>
<td>55 (±16)</td>
<td>SBP, DBP separately</td>
<td>SBP 36%, DBP 22%</td>
<td>mortality</td>
</tr>
<tr>
<td>von Känel et al. 2004</td>
<td>76*</td>
<td>hypertensive, normotensive</td>
<td>36 (±8)</td>
<td>SBP</td>
<td>45%</td>
<td>endothelial dysfunction, atherosclerosis</td>
</tr>
</tbody>
</table>
The predictive value of the dipping phenomenon and the negative prognostic value of blunted nighttime BP drop has been widely accepted (Cuspidi et al. 2004b, Fagard et al. 2008, Verdecchia et al. 1993). Boggia et al. concluded in their large, international database analysis of 7,458 subjects that the nighttime BP was associated with fatal endpoints and the night-to-day ratio predicted total, CV and non-CV mortality (Boggia et al. 2007). In nondipping pattern, for each 10 mmHg rise in nighttime SBP mean the mortality risk has been shown to elevate by 21% (Dolan et al. 2005).

2.4 Dipping - limitations

Although much evidence exists concerning the dipping phenomenon, it has encountered some criticism (Mochizuki et al. 1998). Blunted nighttime BP is influenced by both intrinsic and extrinsic factors that affect both study protocols and the study subjects studied, casting some uncertainty on the concept of dipping.

Firstly, the definition of the dipping phenomenon is not constant. Varying definitions of awake and asleep periods have been used. While some studies use arbitrary nighttime definition according to time in hours, some rely on true sleeping time. The diary of diurnal lifestyle has been pointed out to be crucial for ABPM and dipping definition (Henskens et al. 2008, O’Shea & Murphy 2000). Secondly, the reproducibility of dipping has been questioned and the role of sodium excretion capacity has been suspected behind the dipping phenomenon (Bankir et al. 2008). Furthermore, classifying patients into dippers and nondippers based on a single ABPM recording has been stated to be unreliable (Manning et al. 2000). According toDimsdale et al. the ability to reproduce a consistent dipping pattern has been dismissed in several studies depending on the study population examined (Dimsdale & Heeren 1998). Opposed to the aforementioned findings Hietanen et al. reported a good correlation between repeated 24-hour ABPMs in a healthy Finnish cohort. Both SBP and DBP correlated well between the two ABP recordings repeated at 2-week intervals. Furthermore, simultaneous manual and ABP measurement correlated well, too (0.98) (Hietanen & Wendelin-Saarenhovi 1996).

Hansen et al. have recently analyzed a large pooled data set from previous studies of both hypertensive and randomly recruited subjects. They demonstrate that dipping status and night-to-day BP ratio were significant predictors for outcomes but added little prognostic value over the 24-hour BP level. Pointing out that classification according to night-to-day BP ratio depends on arbitrary criteria
and is poorly reproducible they concluded that the diurnal categorical representations should be supported by continuous analyses adjusted for 24-hour BP (Hansen et al. 2011). It is also noteworthy that both daytime and nighttime BP influence the classification of dipping status (Pickering & Kario 2001).


Obstructive sleep apnea has been independently associated with hypertension (Peppard et al. 2000, Nieto et al. 2000, Fletcher 2001). Episodes of airway obstruction lead to hypoxia followed by hypercapnia and increased sympathetic tone. This promotes vasoconstriction and increases nighttime BP (Wolf et al. 2010). Sleep apnea presumably explains nondipping in a subgroup of both hypertensive and normotensive subjects.

Nighttime measurements have been supposed to elevate BP level because of measurements interfering with nighttime rest. However, the data are controversial (O'Brien 2007, Verdecchia et al. 2007). The present study is based on ABP measurements made with SpaceLabs 90207. According to O'Brien, the SpaceLabs 90207 device does apparently not cause as much sleep disturbances as the older devices (O'Brien 2007). The number of measurements at nighttime is lower than at daytime. This may affect the calculations of nocturnal BP drop.

Nondippers might not be a homogenous group. Some of them have normal daytime BP, but fail to drop the nighttime BP level. Others have high daytime and nighttime BP levels leading to a consistent vascular BP load. On the other hand, the morning surge known to associate with unfavorable CV endpoints is lesser in nondippers and the ischemic damage known to associate with extreme dipping is less pronounced as well (Kario et al. 1996, Kario et al. 2001a, O'Brien et al. 1988, O'Brien 2009). That is why Pickering points out the need for studies based on subjects with the same daytime BP levels to investigate the target organ damages associated especially with nondipping (Pickering 2005).

In conclusion, actimetric measurement is considered the only method capable of distinguishing active/non-active circadian periods. Daily diaries have been
used to record the activity during the 24-period. However, use of diaries has been suspected to contain some uncertainty as well (O’Shea & Murphy 2000). Measures based on at least two ABPM sessions would increase the reliability of the dipping status classification.

2.5 Adiponectin

Adiponectin is a bioactive protein identified in 1996. (Maeda et al. 1996) It is a hormone which belongs to the adipocytokine family secreted by the highly dynamic endocrine organ, the adipose tissue, and is involved in lipid and glucose metabolism. It is present in the serum as a low molecular trimer, medium molecular hexamer or as a high-molecular weight form (HMW). Low serum adiponectin levels are associated with body adiposity and weight (Hara et al. 2006, Li et al. 2011).

2.5.1 Adiponectin and cardio-metabolic risk

Adiponectin acts as an antiatherogenic, anti-inflammatory and insulin-sensitizing agent. It is inversely associated with BMI (Adachi & Brenner 2008). Hypoadiponectinemia has been shown to associate with metabolic syndrome (Hara et al. 2006, Zhuo et al. 2010), left ventricular hypertrophy (Mitsuhashi et al. 2007, Pääkkö et al. 2010), endothelial dysfunction (Tan et al. 2004) and vascular hypertrophy (Matsuo et al. 2007). The association between risk for myocardial infarction and low plasma adiponectin concentrations has been shown (Otsuka et al. 2007, Persson et al. 2010). Pischon et al. found that the association between high adiponectin level and decreased risk of myocardial infarction was independent of traditional CVD risk factors (Pischon et al. 2004). Avery et al. have recently published data concerning the polymorphism of adiponectin gene promoter known to be associated with IMT and atherosclerosis. A common variation in the adiponectin gene was shown to have an effect on SBP (daytime, nighttime and clinical). The effect on DBP was smaller. (Avery P et al. 2011)

High serum adiponectin concentrations have been associated with reduced risk of developing type 2 diabetes or coronary artery disease (Trujillo & Scherer 2005).

Table 4 presents the effect on low adiponectin level and outcome.
Table 4. Hypoadiponectinemia and outcome (based on Schillaci 2007, Li et al. 2011).

<table>
<thead>
<tr>
<th>Target organ</th>
<th>Effect of low adiponectin</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose tissue</td>
<td>Inflammation</td>
<td>prothrombotic state</td>
</tr>
<tr>
<td>Liver</td>
<td>Insulin sensitivity ↓</td>
<td>hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>glucose production ↑</td>
<td></td>
</tr>
<tr>
<td>Vascular smooth muscle cell</td>
<td>proliferation</td>
<td>arterial stiffness</td>
</tr>
<tr>
<td>Endothelium</td>
<td>dysfunction</td>
<td>hypertension, atherosclerosis</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>insulin sensitivity ↓</td>
<td>hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>glucose uptake ↓</td>
<td></td>
</tr>
</tbody>
</table>

### 2.5.2 Adiponectin and blood pressure

Obesity is often accompanied by elevated blood pressure (BP), insulin resistance and hypoadiponectinemia. Lower adiponectin level has been independently associated with diurnal SBP and DBP and blunted nocturnal SBP dipping in obese adults (Shatat et al. 2009). In a large Chinese study (Li et al. 2008) middle-aged hypertensives had significantly lower plasma adiponectin levels than normotensive subjects, and among normotensive subjects the relationship between plasma adiponectin level and SBP depended on the presence of obesity. Low adiponectin level was associated with a higher risk of getting hypertension in a prospective study of Imatoh et al. (Imatoh et al. 2008) Systemic vascular resistance, sodium retention and sympathetic nervous system activity might explain the unfavorable effects of hypoadiponectinemia especially among obese subjects, but the exact biochemical mechanisms between adiponectin and BP regulation still remain to be investigated (Bogaert & Linas 2009, Li et al. 2011).

### 2.6 Metabolic syndrome and ABPM

The relationship between MS and CV morbidity has been shown previously. (Isomaa et al. 2001, Lakka et al. 2002). Several alterations increasing the risk of CVD are often present in MS, e.g. changes in serum lipoproteins, hypertension, hypercoagulation and inflammatory factors.

Elevated circadian BP and nondipping have been associated with MS (Ayala et al. 2009, Hassan et al. 2007, Hermida et al. 2011, Tartan et al. 2006, Vyssoulis et al. 2007, Vyssoulis et al. 2008). In the study of Hermida et al. wrist actigraphy-
verified nondipping pattern was associated with MS in a cross-sectional study of 3,352 non-diabetic hypertensives (Hermida et al. 2011). In a cross-sectional study of Ayala et al. middle-aged, non-diabetic untreated patients with uncomplicated essential hypertension were investigated (n=2,045). MS was present in 40.7%. Wrist actigraphy was used to accurately calculate mean BP during waking and sleeping for each subject. Subjects with MS had significantly higher 24 h mean SBP and a lower mean DBP compared to patients without MS. Both systolic and diastolic nondipping was associated with MS (Ayala et al. 2009). Tartan et al. found that MS score independently predicted a nondipping pattern and higher nighttime BP. MS score was based on numeric grading according to ATP-III (Adult Treatment Panel III) definition consisting of gender, age, hypertension, BMI, triglycerides, HDL-C and fasting glucose (Tartan et al. 2006). However, there are also studies in which the association between MS and blunted nighttime BP has not shown to be significant (Bastos et al. 2007, Cuspidi et al. 2004a, Cuspidi et al. 2005, Foss et al. 2000). Pierdomenico et al. made a meta-analysis of studies concerning ABP measurements in subjects with type 2 diabetics and MS. When analyzing 7 of these studies together, they found that the overall risk ratio for nondipping in MS was 1.19 (95% CI: 1.03–1.374, p=0.018) (Pierdomenico & Cuccurullo 2010).

2.7 Fatty liver and ABPM

Fatty liver is an accumulation of fat in the hepatic parenchyma (macrovesicular steatosis) not due to excess alcohol use. The prevalence of fatty liver is up to 30% in developed countries and nearly 10% in developing countries. Non-alcohol fatty liver disease is the most common liver condition in the world (Smith & Adams 2011).

Although fatty liver is often seen with obesity it also occurs in non-obese subjects and associates with metabolic risk factors (Sung et al. 2009). Kotronen et al. found that liver fat content correlated with intra-abdominal fat more often than with abdominal subcutaneous fat. The total amount of both intra-abdominal and subcutaneous fat was significantly higher in subjects with MS than in subjects without MS independent of age, gender, and BMI (Kotronen et al. 2007). Masaki et al. demonstrated that HOMA index and nighttime systolic ABP were independent factors for high visceral fat in Japanese patients with impaired glucose tolerance (Masaki et al. 2011). Chen et al. showed that nondippers had higher postprandial glucose levels during the OGTT than dippers (Chen et al. 2011).
Insulin resistance has been related to nondipping status, which can be shifted to dipping by treatment with thiazolidinedione in type 2 diabetic patients (Anan et al. 2007). Non-alcoholic fatty liver (NAFLD) has been associated with atherosclerotic carotid artery damage, even in patients without significantly impaired liver function, hypertension or diabetes (Fracanzani et al. 2008, Sookoian & Pirola 2008, Targher et al. 2006, Targher & Arcaro 2007, Hamaguchi et al. 2007).

Hypertensive subjects have been shown to have a significantly higher prevalence of fatty liver compared to normotensive controls (Donati et al. 2004, Lau et al. 2010). Fallo et al. found that a high prevalence of liver steatosis was associated with insulin resistance and low adiponectin levels in essential hypertensive patients with a nondipping profile. Nondipping BP profile was found as a predictor of NAFLD independently of other metabolic factors (Fallo et al. 2008).

Because of the highly elevated risk of metabolic syndrome and remarkably increased CVD risk early noninvasive detection of fatty liver disease is clinically important (Hernaez et al. 2011).

2.8 Renal function and ABPM

High BP exposes the kidney to vascular injury especially when the nighttime BP drop is missing and the organism is prone to a continuous BP load (Timio et al. 1995, Torun et al. 2005). On the other hand, blunted nocturnal BP drop and nondipping pattern is common in nephropathy regardless of the severity of renal failure (Agarwal & Andersen 2005, Tsioufis et al. 2002).

The association between dipping status and renal function has been investigated in several subgroups: normotensive, hypertensive, diabetic, renal transplant patients and subjects with minor or major renal failure. Table 5 shows a summary of these studies addressed in several subgroups. Nondipping is associated with impairments in renal function in most, although not in all, studies.
Table 5. Association between nondipping and renal failure.

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoshide et al. 2003</td>
<td>healthy</td>
<td>no renal damage</td>
</tr>
<tr>
<td>Cuspidi et al. 2004b</td>
<td>hypertensive</td>
<td>no albuminuria</td>
</tr>
<tr>
<td>Farmer et al. 1998</td>
<td>diabetic</td>
<td>progression of nephropathy</td>
</tr>
<tr>
<td>Liu et al. 2003, Tripeti et al. 2005</td>
<td>CKD</td>
<td>CV events, mortality</td>
</tr>
<tr>
<td>Lipkin et al. 1993, Toprak et al. 2003</td>
<td>renal transplantation</td>
<td>LVH</td>
</tr>
<tr>
<td>McGregor et al. 2001</td>
<td>renal transplantation</td>
<td>no association with LVH</td>
</tr>
</tbody>
</table>

2.9 Early atherosclerosis and carotid intima-media thickness (cIMT)

The lumen of the artery is covered by a cell-layer called endothelium. The intima lies under the endothelium, then the media and finally the adventitia as the outermost layer of the artery wall. According to the Malmö Diet and Cancer Study the mean far wall cIMT values for common carotid artery in a middle-aged population (55–65 years) were 0.64–0.88 mm in women and 0.66–0.94 mm in men (Rosvall et al. 2005).

In atherosclerosis the function of the endothelium is disturbed and the intima is slowly thickened by fatty-fibrous deposits narrowing the lumen. Calcification of the fibrous deposits leads to plaques.

Carotid IMT is a marker of atherosclerotic disease. The thickening of the carotid artery can be investigated noninvasively by radiological methods (O’Leary & Polak 2002, Yang & Nambi 2011). For the identification and quantification of subclinical vascular disease and for the evaluation of CVD risk (Stein et al. 2008). US has been widely used in cIMT measurements since 1986 when it was introduced by Pignoli et al. (Dogan et al. 2011, Pignoli et al. 1986).

The association between cardiovascular events and cIMT has been shown in epidemiological studies (Stein et al. 2008). In a prospective study Lakka et al. found that SBP, but not DBP, was associated with cIMT. Even mildly elevated SBP accelerated the progression of preclinical atherosclerosis (Lakka et al. 1999).

In the ELSA study of hypertensive subjects cIMT was more closely related to 24-hour SBP than office BP measurement. cIMT was related to the magnitude of SBP variations. The researchers concluded that the BP variation may enhance tissue growth and atherosclerosis (Mancia et al. 2001, Zanchetti et al. 1998).
The association between cIMT and blunted nocturnal BP drop has been shown (Cuspidi et al. 1999, Pierdomenico et al. 1997, Salvetti et al. 2001).
3 Aims of the study

To evaluate the potential relationship between ambulatory blood pressure measurement values and previously reported markers of cardiovascular disease. The specific aims of each paper were:

1. To study the relationship between ABP measurement values and the plasma adiponectin levels in a middle-aged population-based cohort without diagnosed hypertension (I).
2. To assess the role of nondipping status in the metabolic syndrome in a population-based cohort without diagnosed hypertension or diabetes (II).
3. To study the relationship between ABP measurements and ultrasound-based fatty liver in a population-based cohort consisting of hypertensives and their controls (III).
4. To investigate the association between renal function and dipping pattern in a middle-aged population cohort (IV).
5. To study the relationship between dipping status and carotid intima-media thickness in a population-based cohort consisting of a hypertensive cohort and their control subjects (V).
4 Subjects and method

4.1 Study population

The Oulu Project Elucidating Risk of Atherosclerosis (OPERA) is a randomly recruited population-based epidemiological case-control study aiming to analyze the risk factors and end-points of CVD. The study consists of hypertensive and control cohorts recruited in the city of Oulu, Northern Finland. 600 hypertensive (300 male, 300 female) and 600 age- and sex-matched control subjects were studied. The population consisted of altogether 1,200 subjects, 1,045 of whom participated in the study (86.5% in the hypertensive and 87.7% in the control cohort). The subjects were 40–59 years old at the time of recruitment. The hypertensive cohort was randomly selected from the register of the Social Insurance Institute selecting subjects who had the right to a higher reimbursement class of antihypertensive medication. Age-stratified randomization was made by selecting 15 hypertensive men and 15 hypertensive women from each year of birth (1931–1950). The control cohort was recruited from the national health register including all age-matched inhabitants in Oulu excluding subjects entitled to a refund for antihypertensive medication. The whole study protocol has been previously described in detail (Rantala et al. 1999). Blood samples were collected in the morning after an overnight fast at the research laboratory of the Department of Internal Medicine. All subjects were invited on a separate occasion to 24-hour ambulatory blood pressure measurement, liver ultrasonography and carotid ultrasonography, which was performed within 6–12 months after the laboratory samples. The studies were approved by the Oulu University Ethical Committee. Informed consent was obtained from all study participants. The investigations were conducted according to the principles of the Helsinki Declaration.

The characteristics of OPERA study subjects (n=1,045) are shown in Table 6. Females were slightly older (51.8 vs. 50.7) and had lower gamma-glutamyl transferase. Men used more tobacco and alcohol. There was no difference in BMI, hsCRP and 2-hour oral blood glucose test between the sexes. When the hypertensive and control cohort were compared, BMI, waist circumference, waist-hip ratio, alcohol consumption, amount of smoking, 2-hour oral glucose tolerance test value, triglycerides, creatinine and hsCRP were higher in the hypertensive group.
Table 6. Characteristics of OPERA study subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>male</th>
<th>female</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>520</td>
<td>525</td>
<td>-</td>
</tr>
<tr>
<td>age *</td>
<td>50.7 (40.2-61.0)</td>
<td>51.8 (41.2-62.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI *</td>
<td>27.9 (18.9-44.7)</td>
<td>27.4 (16.9-48.0)</td>
<td>0.083</td>
</tr>
<tr>
<td>waist, cm *</td>
<td>97 (73-139)</td>
<td>84 (61-127)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>waist-hip ratio (SD)</td>
<td>0.93 (0.06)</td>
<td>0.80 (0.06)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>smoking, pack years *</td>
<td>16.3 (0-48)</td>
<td>7.6 (0-46.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>alcohol consumption, g/week *</td>
<td>98.5 (0-732.0)</td>
<td>25.6 (0-297.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>p-cholesterol, mmol/L *</td>
<td>5.8 (3.7-11.3)</td>
<td>5.6 (2.9-10.4)</td>
<td>0.023</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²) (sd)</td>
<td>88 (17)</td>
<td>76 (15)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>s-gamma-glutamyl transferase, µ/l *</td>
<td>58 (9-999)</td>
<td>36 (7-542)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>hsCRP, mg/L *</td>
<td>3.9 (0-103)</td>
<td>3.7 (0-109)</td>
<td>0.567</td>
</tr>
<tr>
<td>fβ-gluk, (mmol/L) *</td>
<td>4.9 (2.0-17.0)</td>
<td>4.6 (3.4-16.0)</td>
<td>0.011</td>
</tr>
<tr>
<td>2-hour blood glucose in OGTT *</td>
<td>5.9 (1.7-23.1)</td>
<td>6.0 (2.2-27.8)</td>
<td>0.588</td>
</tr>
</tbody>
</table>

*min-max

The design in each of the studies I-V according to study group and setting is specified in Table 7.

Table 7. Study designs.

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects (n)</th>
<th>Study groups</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>458</td>
<td>x</td>
<td>ABPM, adiponectin</td>
</tr>
<tr>
<td>II</td>
<td>462</td>
<td>x</td>
<td>ABPM, metabolic abnormalities</td>
</tr>
<tr>
<td>III</td>
<td>890</td>
<td>x</td>
<td>ABPM, fatty liver</td>
</tr>
<tr>
<td>IV</td>
<td>460</td>
<td>x</td>
<td>ABPM, eGFR</td>
</tr>
<tr>
<td>V</td>
<td>900</td>
<td>x</td>
<td>ABPM, cIMT</td>
</tr>
</tbody>
</table>

HT= hypertensive group

4.2 Clinical methods

The participants of the study visited the research laboratory. A questionnaire was completed to collect information about past medical history, current medication, smoking history, alcohol consumption, family history of CVD, physical activity at work and physical activity at leisure. Anthropometric measurements (weight, height, waist, hip) were carried out by trained nurses. BMI was calculated as weight (kg) divided by height squared (m²). Alcohol consumption was calculated after an interview with a trained physician based on the method of Khavari and
Farber (Khavari & Farber 1978) and converted into grams of absolute ethanol used in one week. Smoking was calculated in pack-years (1 pack-year = 20 cigarettes smoked/day in one year). OGTT was performed after overnight fast. Various laboratory tests were taken. The subjects were examined by two physicians with special competence in internal medicine.

4.3 BP measurements

BP was measured according to the recommendations of the American Society of Hypertension. An automatic oscillometric recorder (Dinamap® model 18465X, Criticon Ltd., Ascot, UK) was used for the office BP measurements from the right arm. The measurements were taken in sitting position after at least 5 minutes of rest and measured three times at one-minute intervals. The mean of the second and third measurements was registered as SBP and DBP office value.

Ambulatory BP (I-V) was recorded using the automatic SpaceLabs 90207 oscillometric unit (SpaceLabs Inc., Redmond, Washington, USA) measuring BP every 15 minutes from 4:00 AM to midnight and every 20 minutes from midnight to 4:00 AM. The accuracy and reproducibility of the BP readings obtained with this device have been established (O'Brien et al. 1993). The similarity (difference <5 mmHg) of four Space Labs BP measurements and four auscultatory readings (Y connector) was used to ensure the proper positioning of the cuff. The subjects were asked to relax their arm during the measurement. Values of systolic BP <70 or >250 mmHg, diastolic BP <40 or >150, and HR <40 or >150 beats per minute were automatically excluded from the analysis. Using the above-mentioned criteria fewer than 3% of the BP readings were rejected as artifacts.

Nondipping status was considered as a SBP reduction of less than 10% from daytime to nighttime according to the commonly accepted criteria (O’Brien et al. 1988). The daytime period was defined to start at 6 am and end at 22 pm.

4.4 cIMT measurements

The carotid ultrasonography examination was performed by one single experienced radiologist blinded to the clinical data. A duplex ultrasound system with a 7.5 MHz scanning frequency in B-mode, pulsed Doppler mode and color mode was used (Toshiba SSA-270A, Toshiba Corp., Tokyo, Japan).
During the ultrasonographic examination the patient was lying in a supine position with the head rotated away from the sonographer at an angle of 45°. Each carotid part was examined from anterior oblique and lateral planes, transversally and longitudinally.

The Doppler mode was used to identify the vessels and to evaluate flow disturbances. Each scan of the common carotid artery (CCA) began just above the clavicle and moved past the bifurcation (BIF) and along both the internal (ICA) and external branches as far distally as possible. The procedure was recorded on a Super-VHS videocassette recorder (Panasonic AG-7330, Matsushita Electric Industrial Co., Ltd., Osaka, Japan). The stored video image was measured by one single radiologist approximately one year later from the monitor of the ultrasound device using its electronic callipers.

cIMT was defined as the distance between the media-adventitia interface and the lumen-intima interface. cIMT was measured at five locations on each side, both on the near and the far wall including a total of 20 measurements. Since the near-wall measurement may be difficult to perform accurately (Wikstrand & Wendelhag 1994), only 10 far-wall measurements were used in the analyses. IMT
was therefore measured at five locations on each side: the ICA about 1 cm distal from the BIF, from the BIF and from three locations of the common carotid artery: proximal, middle and distal at about 1–1.5 cm intervals. The most cranial measuring point of CCA was approximately 1 cm proximal from the BIF.

The thickest point of cIMT was searched and measured avoiding sites with atheromatous plaque. The mean of ICA, BIF and the highest three of CCA measurements were defined as the mean cIMT. The intra- and interobserver reproducibility of the IMT measurement was assessed in 31 randomly selected subjects. The repeat measurements were performed from the videotapes 1.5 years after the examination without knowledge of the original results. Variability was estimated by using the mean ± SD absolute difference between paired measurements. The intrareader variability and the correlation coefficient was 3% for the mean IMT and 9.9% for the maximal IMT. Correspondingly, the interreader variability and correlation were 7.2% and 0.93 (mean mode) and 12.8% and 0.92 (maximal mode).

4.5 Laboratory analyses

All of the laboratory test samples were obtained after an overnight fast. Venous blood was drawn into EDTA tubes. Plasma was separated by centrifugation at 2000–2600 rpm for 10 min and kept at 4 °C until further analyses, most of which were done, if possible, within two days after the blood samples had been drawn. Otherwise plasma was stored at −20 °C–−70 °C prior to subsequent analyses. The venous blood glucose concentration was determined with the glucose dehydrogenase method and the plasma insulin concentration with the double RIA method (AIA-PACK IRI, Tosoh Corp., Tokyo, Japan).

The routine clinical laboratory tests were carried out in the Central Laboratory of the Oulu University Hospital and the lipid analyses in the research laboratory of the Department of Internal Medicine by using standard methods.

The concentrations of total cholesterol and triglycerides were determined in the plasma and lipoprotein fractions by enzymatic colorimetric methods (kits of Boehringer Diagnostica, Mannheim GmbH, Germany) using a Kone Specific analyzer (Kone Specific, Selective Chemistry Analyser, Kone Instruments, Espoo, Finland). The VLDL fraction was separated from plasma by ultracentrifugation. After that the HDL fraction was determined from the VLDL-free fraction and the plasma LDL concentration was calculated by subtracting the cholesterol concentration in HDL from that in the VLDL-free fraction (Kervinen et al. 1994).
The coefficients of variation for the determination of plasma total cholesterol, HDL cholesterol and triglycerides were 2.1%, 5.5% and 5.3%, respectively. High sensitivity c-reactive protein (HsCRP) was measured using commercially available ELISA kits with a detection limit of 0.31 ng/mL (Diagnostic Systems Laboratories, Texas, USA).

Plasma adiponectin concentrations were measured with an enzyme-linked immunosorbent assay technique devised in our laboratory (Santaniemi et al. 2006).

A two-hour oral glucose tolerance test (OGTT) with 75 g of glucose was performed for the subjects, and the plasma glucose and insulin levels were determined at 0, 60 and 120 minutes (a glucose-oxidase method, Diagnostica, Merck, Darmstadt, Germany). Plasma insulin concentrations were determined with the double RIA method (a two-site immunoenzymometric assay, Tosoh Corp., Tokyo, Japan). The AUC for glucose (and insulin) in the OGTT was calculated according to Simpson’s rule (Winocour et al. 1992): \[ \text{AUC} = \frac{\text{fasting glucose} + (4 \times \text{glucose60min}) + \text{glucose120min}}{3}. \]

Insulin sensitivity was assessed using fasting plasma insulin concentrations and a quantitative insulin sensitivity check index (QUICKI = 1/\[\log (\text{fasting insulin}) + \log (\text{fasting glucose})]\]) (Katz et al. 2000). The subjects with insulin sensitivity below the lowest quartile of the control cohort (QUICKI < 0.563) were regarded as insulin-resistant.

Type 2 diabetes, IGT and IR were determined according to the WHO criteria (World Health Organization, International Society of Hypertension: Guidelines for the Management of Hypertension). A person was regarded as diabetic if his/her fasting blood glucose was ≥6.1 mmol/L and/or 2h glucose in OGTT was ≥10.0 mmol/L, or if he/she was on diabetes medication (oral or insulin). A subject had IGT if he/she had a fasting blood glucose value <6.1 mmol/L and his/her 2h blood glucose in OGTT was ≥6.7 mmol/L and <10.0 mmol/L.

Serum creatinine was determined with a method based on the Jaffe reaction. The Modification of Diet in Renal Disease (MDRD) formula was used to approximate renal function.

\[ \text{eGFR} \text{ (mL/min/1.73m2)} = 186 \times (\text{serum creatinine in mg/dL}) -1.154 \times (\text{Age}) - 0.203 \times (0.742 \text{ if female}). \]

4.6 Liver ultrasonography

The liver ultrasonography was performed by one single highly experienced radiologist blinded to the clinical data. Liver adiposity was based on liver-kidney
contrast. The examination was carried out using a Toshiba SSA 270 ultrasound system (Toshiba, Tokyo, Japan) with a scanning frequency of 5 MHz. The procedure was captured on a Super-VHS videocassette recorder (Panasonic, Osaka, Japan) and the stored videotapes were analyzed later. Liver brightness was used as the indicator of adiposity and documented by ranging it from 0 to 2 with level 0 indicating normal brightness (non-fatty liver), level 1 indicating medium brightness (moderate lipid accumulation) and level 2 indicating intensely bright liver (severe lipid accumulation). For the final study the subjects were analyzed in two groups, namely non-fatty and fatty liver groups.

4.7 Statistical methods

Statistical analyses were performed with SPSS 16.0 and 19.0 software. Continuous variables were examined and, if necessary, logarithmic transformation was carried out to achieve normal distribution. Categorical variables were summarized as frequencies and percentages, continuous variables as means (± SD) or 95% confidence intervals. The participants were classified as dippers or nondippers according to the night-to-day ratio of SBP. Day-night BP decline less than 10% indicated a nondipping pattern. χ² test was carried out to examine the independence between categorical variables. P-value less than 0.05 was considered to indicate statistical significance.

The study designs are introduced in Table 7. In study I the association between adiponectin and ABP values and dipping was assessed by dividing the study population into tertiles. Analysis of variance was used to test the differences between adiponectin groups. Bonferroni post hoc test was used to find out which groups differed significantly from each other in multiple correlations. Analysis of covariance was used when there was a need to add the continuous predictors (age, BMI, alcohol consumption in grams/week, pack-years of smoking) as covariates. In study II logistic regression was used to predict the occurrence of MS or IGT/T2DM and to assess the independence of each risk factor. Age, sex, smoking habits and dipping were included in equations considering MS. For equations considering IGT/T2DM waist was also included in the model. Results were presented as odds ratios (OR) and 95% confidence intervals.

In study III the association between the liver adiposity groups and dipping pattern was measured by χ²-test. The strength of association between the liver brightness and ABPM values was compared by analysis of covariance adjusted for BMI, age and sex.
In study IV the subjects were analyzed in tertiles based on eGFR. Student t-test or Mann-Whitney U-test was used, as appropriate, to compare the eGFR tertile groups. To study the possible variation in eGFR according to dipping status a general linear model and logistic regression model were used. General linear model was used to define whether renal function is independently associated with the risk of nondipping when adjusted for sex, age, smoking and BMI or QUICKi.

In study V categorical variables were explored with χ²-test to find out the relationship between two categorical variables. One-way analysis of variance was performed to compare the means of dippers and nondippers and analysis of covariance for the adjustment with confounding factors. A multiple linear regression analysis was carried out to define the potential indicators explaining the variance of cIMT. Correlation was tested with partial correlation.
5 Results

5.1 Study subjects (Studies I-V)

5.1.1 Main characteristics

From the whole OPERA study population 900 (86.4%) subjects participated in the 24-hour BP measurement. The characteristics of ABP measured subjects are presented in Table 8.

No statistically significant difference existed between the hypertensive (84.6%) and control (88.2%) group in the participation rate. Subjects who participated in ABPM were slightly older than non-participants. Office heart rate, creatinine, triglycerides and gamma-glutamyl transferase were lower in subjects with ABP measurements performed than in those without.

Table 8. Characteristics of the study subjects according to participation in ABPM.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ABPM*</th>
<th>no ABPM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>900</td>
<td>145</td>
<td>-</td>
</tr>
<tr>
<td>age (y)</td>
<td>51.4 (5.9)</td>
<td>50.3 (6.2)</td>
<td>0.042</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.6 (4.6)</td>
<td>28.3 (4.8)</td>
<td>0.124</td>
</tr>
<tr>
<td>smoking (pack years)</td>
<td>12 (14)</td>
<td>12 (14)</td>
<td>0.861</td>
</tr>
<tr>
<td>alcohol usage (g/week)</td>
<td>61.6 (93)</td>
<td>64.6 (93)</td>
<td>0.721</td>
</tr>
<tr>
<td>BP lowering drug (%)</td>
<td>51.1</td>
<td>57.0</td>
<td>0.184</td>
</tr>
<tr>
<td>office SBP (mmHg)</td>
<td>148 (22)</td>
<td>149 (22)</td>
<td>0.634</td>
</tr>
<tr>
<td>office DBP (mmHg)</td>
<td>89 (12)</td>
<td>89 (12)</td>
<td>0.735</td>
</tr>
<tr>
<td>office heart rate (bpm)</td>
<td>74 (13)</td>
<td>76 (16)</td>
<td>0.025</td>
</tr>
<tr>
<td>creatinine (µmol/L)</td>
<td>82 (15)</td>
<td>88 (78)</td>
<td>0.042</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>82 (17)</td>
<td>84 (20)</td>
<td>0.209</td>
</tr>
<tr>
<td>alt (U/L)</td>
<td>32 (24)</td>
<td>31 (18)</td>
<td>0.734</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>45 (61)</td>
<td>62 (117)</td>
<td>0.007</td>
</tr>
<tr>
<td>total cholesterol*</td>
<td>5.7 (1.0)</td>
<td>5.7 (1.2)</td>
<td>0.905</td>
</tr>
<tr>
<td>LDL cholesterol*</td>
<td>3.5 (0.9)</td>
<td>3.5 (1.0)</td>
<td>0.358</td>
</tr>
<tr>
<td>HDL-cholesterol*</td>
<td>1.3 (0.4)</td>
<td>1.3 (0.4)</td>
<td>0.875</td>
</tr>
<tr>
<td>TG*</td>
<td>1.5 (0.9)</td>
<td>1.8 (1.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>3.6 (7.5)</td>
<td>4.9 (7.0)</td>
<td>0.059</td>
</tr>
<tr>
<td>adiponectin (mg/L)</td>
<td>15.9 (6.9)</td>
<td>15.6 (6.8)</td>
<td>0.592</td>
</tr>
<tr>
<td>QUICKi</td>
<td>0.81 (0.12)</td>
<td>0.60 (0.11)</td>
<td>0.275</td>
</tr>
<tr>
<td>mean IMT (mm)</td>
<td>0.88 (0.19)</td>
<td>0.85 (0.17)</td>
<td>0.058</td>
</tr>
</tbody>
</table>

*mmol/L °SD when appropriate
5.1.2 Blood pressure values

The blood pressure values of the ABP-measured hypertensive subjects (46.6%) and control group subjects (51.4%) are presented in Table 9. The mean office systolic and diastolic BP values of the ABPM participants were slightly above the normal BP limits (148 and 89 mmHg, respectively).

Table 9. ABPM and office values for ABP-measured subjects (n=900).

<table>
<thead>
<tr>
<th>Blood pressure measurement (mmHg)</th>
<th>RR</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office SBP</td>
<td>148</td>
<td>22</td>
</tr>
<tr>
<td>Office DBP</td>
<td>89</td>
<td>12</td>
</tr>
<tr>
<td>ABPM, Daytime SBP</td>
<td>135</td>
<td>15</td>
</tr>
<tr>
<td>ABPM, Daytime DBP</td>
<td>85</td>
<td>9</td>
</tr>
<tr>
<td>ABPM, Nighttime SBP</td>
<td>117</td>
<td>14</td>
</tr>
<tr>
<td>ABPM, Nighttime DBP</td>
<td>70</td>
<td>9</td>
</tr>
<tr>
<td>ABPM, Daytime heart rate (bpm)</td>
<td>74</td>
<td>13</td>
</tr>
<tr>
<td>ABPM, Nighttime heart rate (bpm)</td>
<td>62</td>
<td>9</td>
</tr>
</tbody>
</table>

Nondippers (of total) 26.3%

5.1.3 Main characteristics of dippers and nondippers

Table 10 presents the characteristics according to dipping status. The study subjects consisted of the entire OPERA cohort for whom ABPM and cIMT measurements were recorded (n=900). 51% of the study population was using BP lowering medication. 52% of nondippers were female. Gender, smoking, alcohol consumption, hsCRP, fasting blood glucose, total and LDL-cholesterol, adiponectin or liver enzymes (s-alt, s-ggt) did not differ between the dippers and nondippers. Nondippers (26.3%) were on average older. Their cIMT, triglycerides, BMI and 2-hour OGTT values were higher and quantitative insulin sensitivity index and HDL-cholesterol lower than among dippers. An association between renal function and dipping status existed as nondippers had lower eGFR and higher creatinine than dippers. The office and nighttime DBP and nighttime SBP was higher among nondippers and they used more often BP lowering medication.
Table 10. Characteristics of the study subjects by dipping status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dippers**</th>
<th>Nondippers**</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>663 (73.7)</td>
<td>237 (26.3)</td>
<td>-</td>
</tr>
<tr>
<td>age (y)</td>
<td>51.1 (6.0)</td>
<td>52.2 (5.7)</td>
<td>0.019</td>
</tr>
<tr>
<td>male (%)</td>
<td>50</td>
<td>48</td>
<td>0.602</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 (4.4)</td>
<td>28.5 (4.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>smoking (pack years)</td>
<td>12 (14)</td>
<td>12 (14)</td>
<td>0.989</td>
</tr>
<tr>
<td>alcohol usage (g/week)</td>
<td>61 (91)</td>
<td>65 (99)</td>
<td>0.573</td>
</tr>
<tr>
<td>BP lowering drug (%)</td>
<td>45.9</td>
<td>65.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>fB-gluk (mmol/L)</td>
<td>4.7 (1.3)</td>
<td>4.9 (1.6)</td>
<td>0.059</td>
</tr>
<tr>
<td>OGTT, 2h value (mmol/L)</td>
<td>5.9 (2.8)</td>
<td>6.4 (3.4)</td>
<td>0.018</td>
</tr>
<tr>
<td>Quicki</td>
<td>0.61 (0.1)</td>
<td>0.59 (0.1)</td>
<td>0.024</td>
</tr>
<tr>
<td>total cholesterol (mmol/L)</td>
<td>5.7 (1.0)</td>
<td>5.8 (1.1)</td>
<td>0.176</td>
</tr>
<tr>
<td>LDL -cholesterol (mmol/L)</td>
<td>3.5 (0.9)</td>
<td>3.6 (1.1)</td>
<td>0.288</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.4 (0.4)</td>
<td>1.3 (0.4)</td>
<td>0.019</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.5 (0.9)</td>
<td>1.7 (0.9)</td>
<td>0.012</td>
</tr>
<tr>
<td>creatinine (µmol/L)</td>
<td>81 (14)</td>
<td>84 (17)</td>
<td>0.010</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>83 (16)</td>
<td>79 (17)</td>
<td>0.007</td>
</tr>
<tr>
<td>s-alt (U/L)</td>
<td>32 (23)</td>
<td>33 (25)</td>
<td>0.620</td>
</tr>
<tr>
<td>s-GGT (U/L)</td>
<td>42 (54)</td>
<td>50 (73)</td>
<td>0.081</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>3.4 (6.7)</td>
<td>4.2 (9.3)</td>
<td>0.150</td>
</tr>
<tr>
<td>adiponectin (mg/L)</td>
<td>16 (7)</td>
<td>16 (7)</td>
<td>0.718</td>
</tr>
<tr>
<td>cIMT, mean (mm)</td>
<td>0.88 (0.17)</td>
<td>0.91 (0.23)</td>
<td>0.001</td>
</tr>
<tr>
<td>office heart rate (bpm)</td>
<td>74 (13)</td>
<td>73 (14)</td>
<td>0.481</td>
</tr>
<tr>
<td>office SBP (mmHg)</td>
<td>148 (22)</td>
<td>150 (22)</td>
<td>0.250</td>
</tr>
<tr>
<td>office DBP (mmHg)</td>
<td>89 (12)</td>
<td>90 (12)</td>
<td>0.036</td>
</tr>
<tr>
<td>ABPM day SBP (mmHg)</td>
<td>135 (14)</td>
<td>134 (14)</td>
<td>0.305</td>
</tr>
<tr>
<td>ABPM day DBP (mmHg)</td>
<td>85 (9)</td>
<td>84 (9)</td>
<td>0.095</td>
</tr>
<tr>
<td>ABPM night SBP (mmHg)</td>
<td>113 (12)</td>
<td>127 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABPM night DBP (mmHg)</td>
<td>68 (8)</td>
<td>76 (9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Data are means, when appropriate.  **SD

5.2 Adiponectin and ABPM (Study I)

Study I was aimed to investigate the relationship between ABP and dipping status and adiponectin level in a population of 458 (222 male, 236 female) non-hypertensive, non-diabetic middle-aged controls of OPERA. Adiponectin level was examined in tertiles (low, medium, high) and it was inversely associated with daytime SBP. The association remained after adjustments for age, gender, waist, smoking, alcohol consumption and the quantitative insulin sensitivity check index.
(QUICKi). After analyzing the genders separately, the association between daytime SBP and adiponectin level was seen in women (Figure 3) but not in men. There was no association between adiponectin and systolic nondipping.

Fig. 3. Daytime SBP and adiponectin tertiles in females (n=263). Values are mean (±sd). Non-adjusted.

5.3 Metabolic syndrome (MS) and ABPM (Study II)

Study II was addressed to find out the possible connection between the circadian BP profile and glucose tolerance in middle-aged subjects without diagnosed hypertension or diabetes (n=462) in the control cohort of OPERA.

Nondippers had higher weight and their quantitative insulin sensitivity check index (QUICKi) was lower as a marker of higher insulin resistance. In oral glucose tolerance test (OGTT) the 2-hour blood glucose was higher among nondippers. Subjects with MS were found to have higher heart rate than subjects without MS. When ABPM values were compared between subjects with and without MS both SBP and DBP was higher in subjects with MS at daytime, nighttime and on a clinical visit. (Fig.4) After adjustments with age, sex, smoking
and alcohol consumption an association was seen between metabolic status and higher heart rate, higher office and higher nighttime systolic and diastolic BP. The association between nondipping and MS was statically significant. Subjects with MS were more likely to belong to the group of nondippers also when adjustments with age, sex, smoking and waist circumference were made. The results indicated that nondipping is more frequently seen among subjects with metabolic abnormalities.

Fig. 4. Systolic and diastolic BP values in subjects with (n=108) and without MS (n=354). Values are mean (±s.e.m.). Non-adjusted.

5.4 Fatty liver and ABPM (Study III)

Study III was aimed to investigate the association between fatty liver and ABP measurements in subjects among whom both ABP measurement and liver US examination were available. Altogether 890 OPERA cohort participants were studied. Ultrasound examination was made to determine liver brightness corresponding to liver fat. The study subjects were divided into non-fatty and fatty liver group. 13.9% of subjects with fatty liver showed severe liver brightness. Higher BMI, larger waist, higher triglycerides, higher hs-CRP and lower HDL were seen in the groups of fatty liver. Smoking was more common and the amount of alcohol consumed was higher in the fatty than in the non-fatty liver group. No association existed between office BP and liver brightness. The ABP
values were analyzed after adjusting for sex, age and BMI. 24-hour, daytime and nighttime systolic and daytime diastolic BP was higher in the fatty than the non-fatty group. The significance remained after excluding subjects with alcohol consumption more than 200 g/week. Nondipping did not seem to associate with liver fat.

5.5 Renal function and dipping (Study IV)

Study IV analyzed the potential association between renal function and dipping status in 460 subjects of the OPERA control cohort for whom creatinine measurements and ABPM were available. The mean creatinine concentration was higher among nondippers. After adjustments for age, BMI and sex the association between eGFR and nondipping status remained statistically significant (p=0.032). By linear regression analyses it was found out that dipping status was a predictor of the variation in eGFR (p=0.031) in a similar manner as sex and age. After dividing the study subjects into tertiles according to their eGFR values there was a trend showing that as eGFR decreased, the prevalence of nondipping pattern increased. A logistic regression analysis was constructed to analyze if the eGFR tertiles and nondipping pattern were independently associated. Age, sex, BMI and smoking were included as covariates. When comparing the eGFR tertiles the risk of being nondipper was higher when the renal function was declined, i.e., in the lowest and middle eGFR tertiles, compared to the highest eGFR tertile. The analysis was continued by excluding the subjects with self-reported diabetes, diagnosed coronary heart disease, cerebrovascular disease, antihypertensive medication or lipid-lowering medication. The abovementioned results still remained between the lowest and the highest eGFR also in this subset.

Thus, nondipping seems to associate with higher creatinine concentration and slightly impaired eGFR compared with dippers.

5.6 Carotid intima-media thickness and ABPM (Study V)

In study V the association between ABPM and early atherosclerosis was studied. Early atherosclerosis was defined as intima-media thickness.

After adjustments for age, sex, smoking (pack-years), total cholesterol and office BP, nondipping was associated with a higher mean carotid intima-media thickness (Figure 5). A multiple regression analysis was performed to assess the association between nondipping and cIMT. Sex, age, office SBP, smoking, BMI,
total and HDL cholesterol, triglycerides, use of BP lowering medication and lipid-lowering medication were included in the model as covariates. In conclusion, nondipping was a significant explanatory factor for carotid intima-media thickness. When genders were analyzed separately, nondipping explained cIMT significantly in men, but not in women. The results suggest an association between nondipping pattern and increased cIMT in a randomly recruited, population-based, middle-aged cohort.

*Fig. 5. Dipping status and mean cIMT (±sd).*
6 Discussion

Auscultatory blood pressure measurement is one of the oldest clinical methods, performed for more than a hundred years. The present study explored the circadian BP, especially the dipping phenomenon, in a context with factors known to be involved in cardiovascular morbidity. The study design is cross-sectional and the data were collected during one year. Because of the cross-sectional nature neither causal explanations nor endpoint analyses are possible.

6.1 Study population and design

The OPERA study population was assessed to represent middle-aged Finnish hypertensive subjects and their age and sex-matched control subjects. The present study focuses on subjects among whom the ABP measurement is available. Studies I, II and V focused on the control cohort and studies III and IV on both hypertensive and control cohort. Because the right for reimbursement from the Social Insurance Institute for BP lowering medication was considered as the inclusion criterion for hypertensive cohort (systolic >180/200 mmHg or diastolic >95/105 mmHg), subjects with mild or moderate hypertension were left out from the hypertensive cohort. The control group was aimed to represent Finnish middle-aged population among whom hypertension is also common. When analyzing office BP recordings almost half of the control subjects were hypertensive (i.e. SBP ≥140 mmHg or DBP ≥85 mmHg), which is higher than in a large Finnish cohort study (Terveys 2000).

The participation rate (86.4%) was excellent. The non-ABP-measured subjects were about one year younger and showed higher pulse rate and higher triglyceride levels than the ABP-measured subjects. This may have affected the results by favoring subjects with better metabolic state and more interest in their health. Even so, from a clinical and practical point of view this may not have relevance as a whole.

27% of the male and 24% of the female subjects showed white coat hypertension. The prevalence of white coat hypertension is in harmony with previous findings (Pickering et al. 1988, Pickering 1997, Staessen et al. 1993, Verdecchia et al. 1994).

It has been reported that about 10% of normotensive and about 20% of hypertensive subjects have masked hypertension (Pickering et al. 2002). In our study the prevalence was lower. Masked hypertension was seen in 1.6% (n=7) of
non-treated and in 4.8% (n=22) of antihypertensive-treated subjects. Morning
dosing of the anti-hypertensive medication has been related to masked
hypertension and considered as a promoting factor of the nondipping pattern
(Hermida et al. 2002, Hermida et al. 2005). This is a possible explanation for the
higher incidence of masked hypertension and nondipping status among the treated
subjects. Unfortunately, no information concerning the effect of dosing time is
available for further analyses.

When analyzing the study subjects with ABPM measurements according to
gender men tended to have more CV risk factors. Higher BMI, higher LDL and
total cholesterol, higher triglycerides and lower HDL cholesterol and higher
alcohol consumption were seen among men who in addition were more often
smokers. There was no difference in dipping status between the sexes. The
circadian BP load was higher among men based on 24-hour SBP and DBP values,
but the BP variation based on 24-hour SBP and DBP standard deviations was
higher among women compared to men.

In the present study ABPM recording was taken only in one 24-hour period.
The reproducibility of dipping cannot thus be analyzed. The lack of actigraphy or
diary is a major limitation as asleep-aware BP analysis is not possible. The
interference between the daytime and the nighttime values during the periods of
day/night and night/day margins obviously causes uncertainty in the classification
of dipping/nondipping status. Even so, the nondipping prevalence in this study
does not differ from the prevalence demonstrated in other studies.

The study setting is cross-sectional, which is why causal explanations are not
possible. In the future there is a place for a prospective study with ABP-measured
blood pressure and endpoint registration.

### 6.2 ABPM and adiponectin

In the present study adiponectin was measured as total adiponectin level. It has
been stated that the measurement of high-molecular weight (HMW) adiponectin
(Aso et al. 2006) or the ratio of HMW to total adiponectin level (HMWR) is
preferred to total adiponectin. It has also been stated that this ratio is more closely
associated with insulin sensitivity and metabolic syndrome than high-molecular
weight form (HMW) of adiponectin (Hara et al. 2006, Li et al. 2011). However,
in a recent study of Sumie et al. the total adiponectin levels were significantly
associated with HMW levels (Sumie et al. 2011), indicating that total adiponectin
is as valid as HMW for measuring adiponectin levels.
Abnormal lipid profile and smoking were associated with male gender and men had significantly lower adiponectin levels (p<0.001) compared to women. No differences in BMI (p=0.830) and 2-hour OGTT (p=0.588) value were seen between genders. 24-hour, daytime and nighttime systolic and diastolic BP load was higher in men. In our study the inverse association between daytime SBP and adiponectin level was seen only in females. The mechanism is open to question.

In a cross-sectional study of Kotani et al. (2011) the adiponectin-blood pressure relationship associated with premenopausal, but not with postmenopausal state. It is obvious that in the present study the hormonal state did not affect the adiponectin-SBP association because the female subgroup between the ages of 40 and 59 consisted of both premenopausal and postmenopausal subjects.


The mechanisms between low adiponectin level and high BP are unclear but supposed to associate with impaired endothelium-dependent vasodilatation seen in animal studies. Unfavorable cellular, metabolic and environmental stress conditions surely have an additional effect (Kubota et al. 2002, Chow et al. 2007).

6.3 ABPM and MS

The present study examined nondipping in context with the metabolic syndrome and indicated that nondipping is more frequently seen among subjects with than without MS. This finding is supported by previous research (Fallo et al. 2008, Imatoh et al. 2008, Wang & Scherer 2008, Shatat et al. 2009, Avery P et al. 2011). Also in the studies of Grassi et al. 2008, Vyssoulis et al. 2008, Ayala et al. 2009 and Hermida et al. 2011 nondipping has been suggested to exist more frequently among subjects with MS. The current study is in concert with these findings.

Nondippers are shown to be more often glucose intolerant compared with dippers (Chen et al. 1998). Insulin resistance has been connected to the development of hypertension (Shen et al. 1988, Reaven et al. 1996). The possible mechanism between elevated BP values and MS is supposed to associate with elevated postprandial triglycerides that have a direct effect on endothelial function. Jagla et al. reviewed that dietary fat affects the vasodilative responses and nitric oxide metabolism of endothelium. Endothelin-1, a strong vasoconstrictor, is increased in MS and T2D, promoting atherogenesis and hypertension (Jagla & Schrezenmeir 2001). The effect of MS on circadian BP level is still not clear.
In a recent study of Guerrot et al. circadian pattern of urine excretion (evaluated as the day-to-night ratio of urine flow rate) was explored in subjects with MS. The disturbed urine excretion was associated with reduced nocturnal systolic dipping and reduced glucose-induced insulin secretion. Nondipping was associated with urine excretion independently of age and creatinine level. They concluded that decreased glucose-induced insulin secretion indicates the clinical importance of impaired circadian rhythms in MS (Guerrot et al. 2011).

Furthermore, endothelial dysfunction associates with metabolic disturbances. Perivascular adipose tissue has recently been considered as a biologically active participator in the pathology of CVD. Rajsheker et al. reviewed that perivascular adipose cells exist inside the vascular wall. The endocrinological capacity and released mediators of these cells affect the contractility of the vessel wall. In healthy subjects nitric oxide bioavailability is increased to inhibit the excess vasoconstriction in the vessel wall. In MS the dilator effect is lost and the amount of perivascular adipose cells is increased generating inflammation in the vascular wall. The increasing number of perivascular adipose cells has been associated with cIMT and suggested to stimulate smooth muscle cell proliferation and migration in the vascular wall (Rajsheker et al. 2010).

Sleep apnea is particularly common among middle-aged subjects (Verdecchia 1990, Peppard 2000, Bradley 2009). It has been associated with MS (Vgontzas et al. 2005, Gruber et al. 2006) and elevated sympathetic nervous system activity leading to blunted nocturnal BP dip (Kario 2009). In the present study sleep disorders in concert with the nondipping pattern are an issue for further discussion. Since sleep disorders were not registered in this study it remains unclear to which extent sleep apnea interfered with the BP measurements. The question is of crucial importance because approximately one fourth of the control population fulfilled the MS criteria of the International Diabetes Federation (study II), and one can assume that the amount was even higher in the hypertensive cohort. Nevertheless, the study population consisted of middle-aged subjects among whom sleep apnea is common. Therefore, ABPM in combination with simultaneous polysomnography would have been of great value. However, in clinical practice MS has been stated to be one of the clinical situations in which ABPM is highly recommended (Ayala et al. 2009). Subjects with metabolic disorders benefit from information concerning their nocturnal BP level regardless of possible sleep apnea since high nighttime BP is itself a trigger of CV events. Data in the current thesis do not cause controversy to this statement.
6.4 ABPM and fatty liver

In the present study 24-hour, daytime and nighttime systolic and daytime diastolic BP levels were higher in the fatty liver group compared with the non-fatty group. A trend was seen between nondipping status and liver brightness (p=0.057). Fatty liver is commonly associated with factors similar to MS, forming a cluster of risk factors associated with CV endpoints (Schindhelm et al. 2007, Targher et al. 2006, Targher & Arcaro 2007). However, all patients with NAFLD will not develop MS and vice versa (Targher et al. 2010).

Hypertrophied adipocyte cells in the visceral fat have been associated with fatty liver and cardiometabolic disorders. (Despres & Lemieux 2006) However, a definite quantification of the exact amount of visceral fat is challenging. Increased waist circumference measurement might not alone be sufficient to approximate the amount of visceral fat (Lemieux et al. 2006).

As fatty liver is a state resulting from excess fat accumulating in hepatocytes definite diagnosis can only be achieved by a liver biopsy, which is an invasive method with potential risks. Non-invasive ultrasound examination is accepted as a method to confirm liver adiposity. Even though ultrasound has some inconstancy, it has many advantages when a large cohort is studied. Saadeh et al. compared different radiological methods in observing fatty liver. They found that MRI did not offer any additional advantages over CT or ultrasound in observing fatty liver disease, especially when taking into account wider availability and lower cost (Saadeh et al. 2002). Image-guided proton magnetic resonance spectroscopy has also been used to specify the extent of liver fat (Seppälä-Lindroos et al. 2002). It may be a relevant method when studying a smaller cohort than the present.

Although excess subcutaneous fat may deteriorate the penetration of ultrasound in detecting liver brightness it seems that liver fibrosis does not interfere with adiposity (Palmentieri et al. 2006).

The mechanisms between elevated ABPM values and fatty liver are not clear and thought to be multifactorial. The most evident mechanism consists of unfavorable lifestyle factors, genetic and nutritional factors leading to metabolic disturbances, impaired endothelial function and elevated sympathetic vascular activity (Grassi et al. 2008). This is in concert with the finding of Salvi et al. who investigated the cIMT values of subjects with NAFLD and found that cIMT values were higher in subjects with than without MS (Salvi et al. 2010).

Last but not least, fatty liver is common in MS and obesity, both of which are common in patients with sleep apnea. Epidemiological studies have shown a
significant independent association between obstructive sleep apnea and hypertension (Fletcher 2001, Bradley & Floras 2009). Therefore, the association between sleep disorders and elevated BP has to be kept in mind when evaluating fatty liver in compound with ABPM values.

6.5 ABPM and renal function

In the current study a significant association was found between renal function and nondipping, which is supported by previous findings (Agarwal & Andersen 2005, Agarwal et al. 2009a, Bianchi et al. 1994, Timio et al. 1994, Timio et al. 1995). The mean creatinine concentration was higher among nondippers and risk of being a nondipper was more obvious when eGFR declined, even after adjustments with age, BMI and sex.

The prevalence and incidence of CKD are rising worldwide. The prevalence of nondipping has been reported to increase as well (Agarwal & Andersen 2005, Agarwal et al. 2009a, Farmer et al. 1998). In a retrospective cohort study of An et al. nondipping pattern and LVH were described as predictors of new-onset CKD (An et al. 2011). Since hypertension is a known risk factor for CKD 24-hour BP load is especially deleterious for renal function.

Targher et al. reviewed the accumulative evidence suggesting the independent association between CKD and NAFLD regardless of obesity or hypertension. Because NAFLD occurs both with and without diabetes, they supposed that the inflamed liver tissue releases pro-inflammatory or pro-coagulant mediators as such (Targher et al. 2010). Elevated frequencies of CKD have been found in histologically verified steatohepatitis. Hypertension has been supposed to be the primary mediator (Yasui et al. 2011). CKD and NAFLD have much in common: association with hypertension, association with CVD and difficulties to be diagnosed in the early stage.

Sleep apnea has been associated with increased BP by night (Davies et al. 2000). Patients with CKD often have fluid overload and this may promote sleep apnea, elevate the nighttime BP and turn dippers into nondippers. It has been stated that approximately 50% of subjects with end-stage kidney disease have sleep apnea (Unruh 2007). In addition, according to Agarwal (2009), patients with CKD have more nightly activity, which may partly explain the increased incidence of nondipping among CKD patients. Because of these confounding factors the determination of dipping pattern is undoubtedly demanding among subjects with renal failure.
It is essential to set clear therapeutic targets to prevent the development of CKD in non-diabetic hypertensive patients (An et al. 2011). According to the present study and literature, ABPM seems to have an important role in determining the risk of early renal impairment.

6.6 ABPM and early atherosclerosis

It has been shown that hypertensive subjects have increased IMT values (Bots et al. 1993, Salvetti et al. 2001, Tang et al. 2000). On the other hand, nondipping is associated with the risk of target organ failure among hypertensives (Cuspidi et al. 1999, Cuspidi et al. 2004b, Kario et al. 1996, Pierdomenico et al. 1997, Salvetti et al. 2001, Shimada et al. 1992, Verdecchia et al. 1990). In the present study an association between nondipping pattern and increased carotid IMT was found in a randomly recruited, population-based, middle-aged cohort. This is supported by earlier findings (Mancia et al. 2001, Shintani et al. 2007, Su et al. 2006, von Kanel et al. 2004). When sexes were analyzed separately, an association was seen in men, while only a trend was detected among women. The findings support earlier findings that men exhibit higher diurnal BP load and higher cIMT values compared to women (Khoury et al. 1992, Kotsis et al. 2006, Winberg et al. 1995).

6.7 Clinical relevance of ABPM in detecting cardiovascular risk

Previous findings of BP variation have shown an association with an increased risk of CV events, especially during early morning hours (Brotman et al. 2008, Giles 2005, Muller 1999). In the retrospective case-control PIUMA study morbid CV events were seen more often in nondipper hypertensive women. In men there was no association between outcome and dipping status (P Verdecchia et al. 1993) Furthermore, in a population-based study of Björklund et al. non-diabetic nondipping elderly men did not have increased CV risk or left ventricular hypertrophy (Björklund et al. 2002).

ABPM has a particular role in monitoring the medication to reduce BP variability especially in subjects with several CV risk factors. Women may have an elevated risk for CV events especially associated with high diurnal BP variation compared to men.

Ambulatory BP reduces misdiagnosis and saves costs in diagnosing hypertension; because of this, it is recommended by some authors for most patients before starting antihypertensive drugs (Lovibond et al. 2011). The
additional costs from ABPM are counterbalanced by savings from more targeted treatment. In addition, subjects with white coat hypertension can also be identified and unnecessary antihypertensive medication can be avoided.

The national guidelines require several measurements and calculations of BP means from these measurements. Several patient groups (i.e., the elderly, disabled persons) may not be able to measure their own BP accurately at home. One growing category of patients is the elderly, who are especially prone to drug-induced hypotension and hypoperfusion leading to falls and incapability of living on their own. Without knowledge of nighttime BP levels adjustment of antihypertensive medication is especially demanding in this group. Nighttime heart rate evaluation is also available at the same time. An integrated judgment is needed to tailor the national and international guidelines to suit a particular patient.

Some patients get particularly high clinical benefit from ABP measurement. These are subjects with elevated CV risk factors (i.e., MS, T2D, fatty liver, CKD) and elderly subjects. Old age has been associated with diminished nighttime BP decline (de la Sierra et al. 2009, Kuwajima et al. 1992) and increase in pulse pressure as a sign of vascular aging (Safar et al. 2011). This could affect the definition of dipping pattern. However, in this study aging is not likely to have interfered with calculations because the subjects were at most 60 years of age.

Interestingly, no association between office BP and liver brightness existed in the present study. This points out that subjects with elevated liver adiposity not only exhibit a prehypertensive state, but moreover, will not be identified at a routine clinical visit as subjects having elevated CVD risk.

Subjects with sleep disorders are included in the study population. The components focused on in this study usually overlap with sleep apnea. Controlling sleep apnea is found to be demanding especially in case-control matched studies. Davies et al. (2000) reported that BMI-matched control subjects without sleep apnea were not easy to find. On the other hand, the study population in the current study was from the very beginning planned to consist of a cohort of Finnish middle-aged subjects, and sleep apnea was not a matter of interest when the data were collected. However, it surely has an effect on the results and lacking polysomnography is a clear weakness in the present study. To conclude, subjects with sleep apnea carry an elevated risk of CV morbidity and therefore gain special benefit from specifying the 24-hour BP level to approximate the total risk for cardiovascular morbidity and control the sufficient effect of antihypertensive medication.
6.8 Perspectives for the future

The subjects of the OPERA cohort are 63–82 years at the moment. Further studies concerning the possible hard cardiovascular endpoints would be interesting to explore, especially because of the extensive data already collected from this cohort.

This study highlights the importance of ABPM particularly in subjects with a cluster of CV risk factors. ABPM enables the recording of diurnal BP variation, which is not achieved by office BP measurements. Efforts against continuous BP measurements have been made. Van der Wel et al. have introduced a novel method for recording the continuous office BP. In their investigation the subject was sitting alone in a quiet room for 30 minutes with continuous BP measurement set to take a registration every 5 minutes. Daytime ABPM was included in the study design. When comparing 30-minute continuous BP measurement and daytime ABPM they found that 30-minute office BP measurement agreed well with daytime ABPM and detected white coat and masked hypertension as well as ABPM (van der Wel et al. 2011). This method is additive, and presumably more valid for defining BP level. However, it is not possible to get nocturnal BP values with this equipment, either.

The present study is targeted for conditions commonly seen in concert with metabolic disorder. In addition, the role of sleep apnea, autonomic dysfunction and salt sensitivity has special importance in elevating nighttime BP although they were not explored in the current study. At the moment ABPM is the only tool to get information of nighttime blood pressure level that is worthy of attention in clinical practice as a sensitive predictor of cardiovascular outcome (O’Brien 2000, Dolan 2005).
7 Conclusions

1. Adiponectin has been shown to associate with metabolism and endothelial function. In the present study high adiponectin level was in association with low daytime SBP especially in women. Further studies will show whether clinical availability of adiponectin measurement would help to identify subjects with elevated CV risk.

2. Elevated circadian BP values and nondipping seems to associate with metabolic disturbances. In the present study nondipping was linked to high weight, insulin resistance and MS. According to this, especially patients with impaired glucose metabolism would benefit from ambulatory BP measurement.

3. Risk for cardiovascular morbidity is associated with fatty liver, which is a state often combined with smoking, alcohol consumption, high BMI, wide waist, elevated triglycerides, elevated CRP and low HDL. In the present study fatty liver was associated with elevated daytime and nighttime systolic ABPM levels. Therefore, the BP level of subjects with fatty liver should be carefully examined.

4. Even minor renal function impairment is associated with nondipping. Dipping status seems to predict the variation in eGFR. Shifting nondipping pattern to dipping pattern by optimizing the antihypertensive medication is of special value among subjects with renal deterioration. ABPM is an accurate tool for this purpose.

5. The risk of arterial wall damage is elevated when the diurnal BP load is high. In the present study increased carotid intima-media thickness was related to nondipping pattern especially in men. Nondipping is associated with a cluster of CV risk factors. High nighttime BP load and nondipping status affect the vessel wall and increase the risk of atherosclerosis.

6. The present study lacked a diary or actimetric recording. Another major deficiency was the lacking data on sleep apnea. This calls for future studies. The possible sleep apnea definition should be included in the research arrangement when ABPM is performed. It is also essential to record the circadian activity. Taken these restrictions into account, a study focusing on blunted nocturnal BP and CV endpoints in this cohort would be of great interest.
References


Original publications


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Original publications are not included in the electronical version of the thesis.
1174. Länsä, Virpi (2012) Regulation of murine hepatic Cytochrome P450 2a5 expression by transcription factor Nuclear factor (erythroid-derived 2)-like 2
1176. Puljula, Jussi (2012) Alcohol-related traumatic brain injuries before and after the reduction of alcohol prices : Observations from Oulu Province and Northern Ostrobothnia
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AMBULATORY BLOOD PRESSURE

ASSOCIATION WITH METABOLIC RISK INDICATORS, RENAL FUNCTION AND CAROTID ARTERY ATHEROSCLEROSIS

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