JAANA JOKINIITTY

Ambulatory Blood Pressure and Blood Pressure Responses to Tests in Predicting Future Blood Pressure Level and Left Ventricular Mass after 10 Years of Follow-Up

■

ACADEMIC DISSERTATION

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To my close ones

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ABBREVIATIONS

Adj.R^2	adjusted coefficient of determination
ACE	angiotensin converting enzyme
ANOVA	analysis of variance
ASE	the American Society of Echocardiography convention
BHT	borderline hypertensive
BMI	body mass index
BP	blood pressure
BSA	body surface area
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CV	cardiovascular
DBP	diastolic blood pressure
ECG	electrocardiography
FS	fractional shortening
h	hour
HG	isometric exercise (hand grip)
HR	heart rate
HT	hypertensive
IAMB	intra-arterial ambulatory blood pressure monitoring
IVST	interventricular septal thickness at end-diastole
LV	left ventricular
LVEDD	left ventricular internal dimension at end-diastole
LVESD	left ventricular internal dimension at end-systole
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVMI	left ventricular mass index
LVPWT	left ventricular posterior wall thickness at end-diastole
MAP	mean arterial pressure
NT	normotensive
N	number
Rec	recovery period after dynamic exercise test
ROC	receiver operator characteristic curve
RV80	80% range of variability from cumulative distribution curve (90^{th}-10^{th} percentile)
RWT	relative wall thickness
SBP	systolic blood pressure
SD	standard deviation
W	watts
WL2	work load 2 at dynamic exercise test
WLL	last work load at dynamic exercise test

INTRODUCTION

Hypertension is recognized worldwide as a major public health problem. In the United States, it is estimated that 43 million Americans have hypertension, which is defined as a systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg and/or taking antihypertensive medication (Burt et al. 1995b). The percentage of hypertensive adults with controlled hypertension has increased from 11% to 24% when comparing the separate national surveys in the United States during 1976-1980 and 1988-1991. Despite the improvement, over 70% of the hypertensive subjects have imperfect control of hypertension (Burt et al. 1995b). Consequently, the age-adjusted stroke mortality rates have been reported to have risen slightly, and the rate of decline of coronary heart disease (CHD) mortality has been found to decrease in the United States (WHO Guidelines Subcommittee 1999).

In Finland, the FINMONICA project (Monitoring trends and determinants In Cardiovascular disease in Finland) has performed four independent, cross-sectional population surveys between 1982 and 1997 (National Public Health Institute 1982). The total number of participants has been 27 623. The results have shown that the blood pressure (BP) level in men and women aged 25-64 years remained fairly stable in Finland between 1982 and 1987, whereas during 1987-1992 a significant decline in BP levels was detected in all study areas (Kastarinen et al. 1998). Between 1992 and 1997, DBP has remained unchanged, but the mean SBP has decreased further. During the 15 years of follow-up the proportion of hypertensives with adequately controlled BP (< 160/95 mmHg) has increased from 9.4% to 23.5% in men and from 16.0% to 36.7% in women. Thus, the control of hypertension is still far from optimal.

Takala et al. (2001) have also examined recently the control of hypertension among 1782 subjects within the public health care in Finland. The mean age of the men was 61 years and of the women 64 years. They found that only 19% of the men and 20% of the women had good control of hypertension (< 140/90 mmHg). Satisfactory control of hypertension (< 160/90 mmHg) was achieved in 37% of the men and 41% of the women. Combination therapy led more often to good control of hypertension than monotherapy.

Because cardiovascular (CV) drugs compose one of the most expensive drug group, they have a huge economical impact both nationally (Lääkelaitos ja Kansaneläkelaitos 2001) and internationally. In Finland, 464 132 subjects had special refund for antihypertensive medication in 2000. When comparing the refunds of different antihypertensive drugs, 58% of the subjects used ß-blockers, 48% agents acting on renin-angiotensin system, 33% diuretics and 35% calcium channel blockers. Special refund of medicines amounted in 2000 to FIM 2.7 billion, of which the antihypertensive medicines accounted for 28%.

Thus, hypertension is a serious problem, contributing to the most common causes of morbidity and mortality. Any improvement in the recognition of high BP and preventing hypertension-related target-organ damage is of great importance. One of the most important signs of preclinical disease is left ventricular hypertrophy (LVH), the diagnosis of which may improve the management of hypertensive subjects by defining those who will truly benefit from the treatment of high BP. The present study will clarify if the predictive value of casual BP measurements on future BP level, need for antihypertensive medication and LVH could be improved by using ambulatory BP monitoring and BP responses to tests. That will contribute both to the better and earlier diagnosis of hypertension and LVH and, on the other hand, avoid unnecessary treatment of those who do not need therapy.

REVIEW OF THE LITERATURE

1. Influence of personal characteristics and lifestyle measures on blood pressure

1.1 Age and blood pressure

It is well established that especially among Western populations BP tends to increase progressively with age (Burt et al. 1995a). Average increases of 20 mmHg in SBP and 10 mmHg in DBP from the age of 30 years to the age of 65 years have been noted in the Framingham Heart Study cohort (Kannel 1996). In that population, SBP continued to rise until age of 80 years for women and 70 years for men, whereas DBP increased until age of 60 years for women and 55 years for men, and then started to decline. Thus, in the elderly the isolated systolic hypertension accounted for 65-75% of the hypertensive cases. Although there is ample evidence of an increase in BP with age (Kotchen et al. 1982, Lakatta 1989), there is also evidence that this hypothesis is valid only in populations with a high intake of salt and fatty acids, or an increase in body weight by age (Oliver et al. 1975, Page et al. 1981, Carvalho et al. 1989, Pavan et al. 1997).

1.2 Body weight and blood pressure

Increased body weight has been found to associate closely with elevated BP (Dyer et al. 1989). In the Framingham Heart Study, 70% of the hypertension in men and 61% in women was directly attributable to excess adiposity, with an average of 4.5 mmHg increase in SBP for every 10-pound weight gain (Kannel

et al. 1993). Also other prospective studies have shown a strong influence of weight on hypertension (Paffenbarger et al. 1968, Haffner et al. 1992, Ascherio et al. 1996, Stamler et al. 1997, Huang et al. 1998, Wilsgaard et al. 2000). On the other hand, Phase II of the Trials of Hypertension Prevention (TOHP II) concluded that a linear relationship existed between reduction in weight and reduction in BP; for every one kilogram of body weight lost SBP reduced by 0.45 mmHg and DBP by 0.35 mmHg (Stevens et al. 2001). The effect of weight loss on the reduction of BP has been confirmed also by other studies (MacMahon et al. 1987, Cutler 1991, Bao et al. 1998, Whelton et al. 1998, He et al. 2000).

1.3 Dietary contents and blood pressure

Epidemiologic evidence has shown that primitive populations who do not use dietary sodium have no hypertension, but when they increase their sodium intake their BP rises (Poulter et al. 1990). Even short periods of increased sodium intake have been found to raise BP also in normotensives in industrialized countries (Mascioli et al. 1991). Cutler et al. (1997) have published an overview of 32 trials including 2635 subjects concerning the effects of reducing sodium intake on BP. They concluded that 100 mmol/24h of sodium reduction resulted in a decrease of BP by 5.8/2.5 mmHg in hypertensives, and by 2.3/1.4 mmHg in normotensives. Evidence for a positive relationship between salt restriction and reduction in BP has been accumulative (Law et al. 1991, Whelton et al. 1998, He et al. 2000).

Caffeine has been found to acutely elevate BP (Freestone and Ramsay 1982), but caffeine ingestion has not been associated with an increased incidence of hypertension (Myers 1988, Salvaggio et al. 1990). However, limiting caffeine intake may be desirable in hypertensive patients, because BP has been found to

significantly decrease during abstinence and, on the other hand, to increase during coffee drinking after a 2-week intervention using 24-hour ambulatory BP monitoring (Rakic et al. 1999). In addition, caffeine has been reported to potentiate the rise in BP induced by work related stress (Jeong and Dimsdale 1990).

Low dietary potassium intake has been suggested to be a risk factor for the development of hypertension (Linas 1991) and, on the other hand, increased potassium intake has been reported to reduce BP (Linas 1991, Barri and Wingo 1997, Whelton et al. 1997) and the need for antihypertensive medication (Siani et al. 1991). Calcium supplementation has also been reported to cause a small reduction in SBP, but not in DBP (Allender et al. 1996, Bucher et al. 1996). However, the effect has been too small to support the use of calcium supplementation for preventing or treating hypertension. Furthermore, 6 years of follow-up of 7731 participants has shown an inverse relationship between serum magnesium and incidence of hypertension, whereas no association was found between dietary magnesium and incidence of hypertension (Peacock et al. 1999).

Appel et al. (1997) have examined the effects of dietary patterns on BP by a diet rich in fruit, vegetables and low-fat dairy foods, and with reduced saturated and total fat among 459 adults. They concluded that after 8 weeks of diet, SBP reduced by 2.8 – 5.5 mmHg more and DBP by 1.1 – 3.0 mmHg more than in the control group although sodium intake and body weight were maintained at constant levels. In addition, in the study of 354 participants in the Dietary Approaches to Stop Hypertension (DASH) trial the diet that emphasized fruit, vegetables and low-fat dairy products lowered BP significantly more in hypertensives than in normotensives (Moore et al. 1999). In overweight hypertensive subjects, dietary fish has also had a significant and independent

effect on 24-hour ambulatory BP even after adjustment for weight, urinary sodium, potassium and dietary macronutrients (Bao et al. 1998).

1.4 Alcohol consumption, smoking and blood pressure

Alcohol intake has been found to be a significant predictor of hypertension (Dyer et al. 1981, Gordon and Kannel 1983, Ascherio et al. 1996, Tsuruta et al. 2000). It has been estimated that up to 11% of cases of hypertension in men and 1% in women in industrialized countries are due to excess alcohol ingestion (MacMahon 1987). Some have suggested a linear relationship throughout the entire range of alcohol consumption and BP (Vriz et al. 1998), whereas others have found a J-shaped relationship showing higher BPs in non-drinkers than in light drinkers (Gordon and Kannel 1983, Kaplan 1995). Seppä et al. (1994) have concluded that hypertension is more common among those who drink alcohol daily than episodically. In addition, regular use of alcohol has been associated with poor compliance with antihypertensive medication (Tuomilehto et al. 1984). Reduction of alcohol intake has been found to contribute to the fall in BP (Puddey et al. 1987, Puddey et al. 1992), but recurrent BP elevation has been seen if alcohol intake has been restarted (Kaplan 1995).

Smoking can repeatedly produce a transient rise in BP of approximately 10/8 mmHg (Freestone and Ramsay 1983). No tolerance has been found to develop to the pressor effect of nicotine (Verdecchia et al. 1995a). On the other hand, the effect of each cigarette has been shown to vanish during abstinence, making it possible that the pressor effect may be missed when casual BP is measured (Mann et al. 1991, Verdecchia et al. 1995a). Indeed, habitual smokers generally have had even lower BPs than non-smokers, which has been suggested to be due to their lower weight (Gordon and Kannel 1983).

1.5 Physical activity and blood pressure

Exercise training has been shown to decrease BP in approximately 75% of hypertensive individuals, with systolic and diastolic BP reductions averaging approximately 11 mmHg and 8 mmHg, respectively (Hagberg et al. 2000). Reductions in BP have been found to be independent of changes in body weight or body composition (Kokkinos and Papademetriou 2000). Recent findings have also suggested that low-to-moderate-intensity exercise (35% to 79% of age-predicted maximum heart rate (HR) or 30% to 74% of maximal oxygen uptake) may be more effective in lowering BP than higher-intensity exercise (Halbert et al. 1997, Kokkinos and Papademetriou 2000). On the other hand, a meta-analysis of 29 studies concluded that exercising more than three times per week had no additional impact on BP reduction (Halbert et al. 1997). Reductions in BP have been observed already after 1 to 10 weeks of exercise training (Hagberg et al. 2000).

2. Hypertension

There is no specific level of BP where CV and renal complications start to occur; thus the definition of hypertension is arbitrary but, on the other hand, needed for practical reasons in patient assessment and treatment (Carretero and Oparil 2000). The correlation between BP and the risk of CV diseases, renal disease, and mortality has been shown to be strong, positive and continuous, even in the normotensive range (Carretero and Oparil 2000).

2.1 Types of hypertension

Essential, primary, or idiopathic hypertension is defined as high BP in which secondary causes such as renovascular disease, renal failure, pheochromocytoma, aldosteronism, or other causes of secondary hypertension are not present. It has been estimated that essential hypertension accounts for 95% of all cases of hypertension. It has also been suggested that essential hypertension is a heterogenous disorder, with different patients having different causal factors that lead to high BP (Carretero and Oparil 2000).

2.2 Physiology of essential hypertension

Usually, clinical hypertension is classified on the basis of SBP and DBP, although these two BP values represent only the limits between which arterial BP fluctuates during a cardiac cycle (Safar 1999, Safar and London 2000). Physiologically BP curve should be described as involving two different components: a steady component, mean blood pressure (MAP; calculated as DBP plus one-third of pulse pressure, PP), and a pulsatile component, PP (the difference between SBP and DBP) (Safar 1989, London and Guerin 1999, Mitchell et al. 1999). The level of MAP has been found to be the same in all parts of the arterial tree, whereas PP is known to be of greater amplitude in peripheral than in central arteries (Safar 1989, Safar 1999, Dart and Kingwell 2001). It has also been suggested that PP is not explicable by any single, simple model of circulation, while MAP is adequately described by cardiac output and total peripheral resistance (Dart and Kingwell 2001, Safar 2001). The main factors influencing PP have been shown to be the velocity of left ventricular (LV) ejection, the visco-elastic properties of the arterial wall, and the wave reflection that occurs throughout the arterial tree (Safar et al. 1989, Safar and London 2000, Dart and Kingwell 2001). Thus, for a given cardiac output, the

level of PP is influenced principally by the status of the large arteries, whereas the level of MAP is more influenced by the degree of reduction in the calibre of the small arteries (Safar et al. 1989, London and Guerin 1999, Safar and London 2000). The increase in large artery stiffness resulting from fragmentation and disruption of elastic lamellae and alteration in the collagen to elastin ratio have been suggested to be of profound importance to the genesis of increased PP with age (Avolio et al. 1998). On the other hand, in young subjects with systolic hypertension, increased LV ejection is usually considered the most important factor explaining increased PP (Safar et al. 1989, Safar and London 2000). Alterations in the buffering function of the large arteries, as indicated by decreased compliance, have been found to participate in the increased afterload in hypertensive patients and thus influence the degree of cardiac hypertrophy (Safar et al. 1987, Dart and Kingwell 2001). Concerning BP components, increased SBP and PP have been shown to favor LVH, while lower values of DBP have been found to be a potential limiting factor to coronary perfusion (Safar and London 2000, Dart and Kingwell 2001).

2.3 Borderline hypertension

It has been suggested that individuals with borderline hypertension are more likely to progress to established hypertension than those with normal BP values. A 26-year follow-up of 5209 individuals from the Framingham Heart Study showed that the probability of individuals with high-normal BP developing hypertension was double to threefold higher that of those with normal BP (Leitschuh et al. 1991). Thus, the authors concluded that individuals with high-normal BP should be followed-up with frequent BP measurements and counseled on modification of risk factors of hypertension. Recently, Vasan et al. (2001) have performed a 4 years of follow-up to establish the best frequency of BP screening by assessing the rates and determinants of progression to

hypertension among 9845 subjects with optimal, normal and high-normal BP values. Their findings indicated that 37-50% of the participants with high-normal BP and 16-18% with normal BP developed to hypertension after only 4 years of follow-up. Thus, they concluded that the optimum BP screening interval might be once a year for individuals with high-normal BP and every two years for those with normal BP. De Faire et al. (1993) have also examined the prediction of BP of 143 borderline hypertensive 35- to 45-year-old men. They found that after 1 year of follow-up 14.7% of the men had developed established hypertension, 67.8% remained within the borderline range, whereas 15.7% had become normotensive. In addition, the previous results of our study group have shown that 70% of the normotensives and 86% of the hypertensives were still in their initial classification group, but 67% of the borderline hypertensives had become hypertensive after 5 years of follow-up (Majahalme et al. 1996).

3. Predictive value of blood pressure

3.1 Diastolic blood pressure

Epidemiological evidence has shown BP to be a strong and consistent predictor of the development of CHD, stroke, transient ischemic attack and congestive heart failure (CHF) (Stokes et al. 1989). In the past, DBP has been regarded as the most important factor of adverse sequelae of hypertension (Goodridge 1927, Report of the Joint National Committee 1977). MacMahon et al. (1990) made a meta-analysis of nine major prospective observational studies, and the combined results demonstrated positive, continuous and apparently independent associations of DBP with stroke and CHD. The meta-analysis showed that

prolonged decreases in DBP of 5, 7.5 and 10 mmHg were associated with at least 34%, 46% and 56% decreases in the risk of stroke and at least 21%, 29% and 37% decreases in the risk of CHD, respectively.

3.2 Systolic blood pressure

Although it has been over three decades since SBP was first identified as a better predictor of CHD events and strokes than DBP (Gubner 1962, Morris et al. 1966, Kannel et al. 1969b, Kannel et al. 1970, Kannel et al. 1971, Kannel 1974), it has only been within the past 10 years that worldwide guideline committees have first drawn attention to the problem of elevated SBP as a predictor of CV risk (The fifth report of the Joint National Committee 1993). Since then, several major prospective studies have indicated that SBP is a more powerful predictor of risk of CHD, stroke and renal disease than DBP (He et al. 1999).

Data from 30 years of follow-up of the Framingham Study cohort showed that in individuals with systolic hypertension, DBP was only weakly related to the risk of CV events, but in those with diastolic hypertension the risk of such events was strongly influenced by the level of SBP (Stokes III et al. 1989). The Multiple Risk Factor Intervention Trial (MRFIT) also suggested that SBP was a stronger predictor of risk of death from CHD and stroke than DBP (Neaton and Wentworth 1992, Stamler et al. 1993). When they divided the baseline SBP and DBP levels into deciles, the relative risk of CHD mortality was 3.7 for SBP and 2.8 for DBP when comparing the relative risks of the highest versus the lowest decile. The relative risk of stroke mortality of the highest versus the lowest decile was 8.2 for SBP and 4.4 for DBP, respectively. In the Copenhagen City Heart Study, 19 698 women and men were followed for an average of 12 years, and the results showed that SBP was a more important

predictor of stroke than DBP (Lindenstrom et al. 1995). Compared with normotensive individuals, the relative risks of stroke were 1.3, 3.2 and 4.1 in women and 1.4, 2.3 and 2.9 in men, for isolated diastolic hypertension, combined systolic and diastolic hypertension and isolated systolic hypertension, respectively.

In addition, in the MRFIT cohort of 332 544 men, the estimated risk of end-stage renal disease was associated with elevations of SBP more closely than with DBP during an average of 16 years of follow-up (Klag et al. 1996). When BP components were included in a Cox proportional hazards model, SBP that was higher by 1 SD (15.8 mmHg) was associated with a relative risk of 1.6 for end-stage renal disease and a 1 SD (10.5 mmHg) increase in DBP was associated with a relative risk of 1.2, respectively.

The Systolic Hypertension in the Elderly Program (SHEP) was the first study to demonstrate that a reduction of SBP in older persons with stage 2 or 3 isolated systolic hypertension (SBP $\geq$ 160 mmHg and DBP < 90 mmHg) resulted in reduced morbidity and mortality (SHEP Cooperative Reseach Group 1991). During an average follow-up of 4.5 years, all CV events reduced by 32% and stroke incidence by 36% in the active treatment group. More recently, the Systolic Hypertension in Europe (Syst-Eur) trial (Staessen et al. 1997d) and the Systolic Hypertension in China (Syst-China) trial (Liu et al. 1998) have also demonstrated the benefits of antihypertensive medication among elderly patients with isolated systolic hypertension.

3.3 Pulse pressure

Darne et al. (1989) have provided the initial epidemiological evidence that PP is a CV risk factor independent of MAP among women older than 55 years. Since

then, there has been increasing evidence of the significance of PP as an independent risk factor of CHD (Madhavan et al. 1994, Mitchell et al. 1997, Millar et al. 1999), CHF (Chae et al. 1999) CV mortality (Domanski et al. 1999b) and total mortality (Mitchell et al. 1997, Domanski et al. 1999a, Domanski et al. 1999b).

Benetos et al. (1997) have investigated the relationship of PP to CV mortality in 19 083 men 40 to 69 years old, and they concluded that a wide PP was a significant independent predictor of all-cause, CV and coronary mortality after 19.5 years of follow-up. Data from the Framingham Heart Study population have also shown that in middle-aged and older individuals the CHD risk was inversely related to DBP at any given SBP of ≥ 120 mmHg, suggesting that a higher PP was an important component of risk (Franklin et al. 1999). Neither SBP nor DBP was superior to PP in predicting CHD risk after a mean follow-up of 14.3 years. On the other hand, Sesso et al. (2000) have found that PP predicted best the risk of CHD among older men, whereas among younger men PP did not add to the predictive value of MAP.

Concerning the prospective value of ambulatory BP monitoring, Verdecchia et al. (1998b) have shown that ambulatory PP was a marginally better predictor of total CV risk than casual PP among 2010 individuals with uncomplicated essential hypertension after a mean of 3.8 years of follow-up.

3.3.1 Pulse pressure and left ventricular hypertrophy

Very few studies so far have evaluated the relationship between PP and LVH as a target-organ damage in hypertension and none of them has been prospective in nature. Pannier et al. (1989) have reported, in their cross-sectional study of 11 normotensive and 36 hypertensive subjects, that the increased PP in

hypertensive subjects might influence the development of cardiac hypertrophy independently of MAP and aortic distensibility. Baguet et al. (2000) have also found in a cross-sectional study of 61 never treated hypertensive subjects, that PP was the BP parameter that best correlated to LV mass (LVM). In addition, a retrospective 9.4 years of follow-up of 140 hypertensive subjects has shown that 24-hour ambulatory intra-arterial PP correlated best to LVM (Khattar et al. 1997).

4. Predictive value of ambulatory 24-hour mean blood pressure

4.1 Prediction of blood pressure level and need for antihypertensive medication

There is only little evidence that ambulatory mean BP better predicts future BP level than casual BP. Palatini et al. (1994) have performed two non-invasive 24-hour ambulatory BP recordings three months apart in 508 hypertensive subjects and found that reproducibility was better for ambulatory than for casual BP. It was also greater for 24-hour than for daytime BP and lowest for night-time BP. Majahalme et al. (1996a) have also shown that 24-hour ambulatory intra-arterial mean SBP added 4% to the predictive power of casual SBP for future ambulatory SBP after 5 years of follow-up. However, the prediction of future ambulatory DBP and casual SBP or DBP was not improved by 24-hour mean BPs. In addition, Staessen et al. (1997) have compared casual and ambulatory BP measurements in the management of hypertensive patients. They found that adjustment of antihypertensive treatment based on ambulatory 24-hour BP, instead of casual BP, led to less intensive drug treatment with still

preservation of BP control, general well-being and inhibition of LV enlargement but did not reduce the overall costs of treatment.

4.2 Prediction of left ventricular hypertrophy and overall cardiovascular risk

We also lack definite prospective data assessing the predictive value of ambulatory BP compared with casual BP for CV damage and other hard end-points (Stanton 1999, Mancia and Parati 2000). Data from the cross-sectional studies have shown that LVH is more closely associated with ambulatory than with casual BP (Gosse et al. 1986, Parati et al. 1987, Majahalme et al. 1996b, Muiesan et al. 1996, Boley et al. 1997, Diamond et al. 1997, Tsioufis et al. 1999) but, on the other hand, the closeness of the association between casual BP and LVH has been found to increase with the number of casual BP measurements and visits to a clinic (Fagard et al. 1997c, Jula et al. 1999, Verdecchia et al. 1999). The mean weighted correlation coefficients for the relationship of LVM with ambulatory 24-hour SBP/DBP have usually been 0.50/0.44 and with casual SBP/DBP 0.35/0.32, respectively (Verdecchia et al. 1999).

Concerning prospective evidence, Fagard et al. (1997b) have analysed the relationships between changes in LVM in response to 6-month antihypertensive therapy and changes in casual BP, average 24-hour ambulatory BP and daytime and night-time BPs. They concluded that the average 24-hour BP added 6.2 – 7.4% to the predictive value of casual SBP, and 11.2 – 14.5% to the predictive value of casual DBP, respectively. The abilities of casual and ambulatory BP have also been compared in the prediction of LVH and carotid atherosclerosis in 295 uncomplicated hypertensive patients after a mean of 10.2 years of follow-up (Khattar et al. 1999). The analyses showed that age, 24-hour mean SBP and

BMI were independent correlates of LVH, whereas age, 24-hour PP and pack years of smoking were independent predictors of carotid atherosclerosis. In addition, in the Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation (SAMPLE), regression of LVH after 12 months of antihypertensive treatment was predicted much more closely by treatment-induced changes in ambulatory 24-hour average BP than in casual BP (Mancia et al. 1997b).

The Ohasama study was the first to show that 24-hour BP predicted CV and all-cause mortality better than casual BP in the general population (Imai et al. 1996, Ohkubo et al. 1997a). In addition, in the Syst-Eur study in older patients with isolated systolic hypertension, ambulatory 24-hour SBP, when exceeding 142 mmHg, was a significant predictor of CV complications over and above casual SBP (Staessen et al. 1999).

5. Predictive value of short-term ambulatory blood pressure recording

5.1 Prediction of blood pressure level and need for antihypertensive medication

Some authors have proposed that the average of a few shorter BP monitoring periods could be a useful substitute for daytime or 24-hour BP monitoring (Weber et al. 1982, Clement et al. 1984, Sheps et al. 1994). However, all of these studies have been cross-sectional in nature indicating that the predictive value of the short-term recordings on future BP level is still lacking.

5.2 Prediction of left ventricular hypertrophy and overall cardiovascular risk

The first large prospective study, based on daytime ambulatory BP readings, investigated the value of ambulatory BP in 1076 hypertensive individuals in the prediction of CV events after a mean of 5 years of follow-up (Perloff et al. 1983). The patients were classified according to whether ambulatory BP was higher or lower than predicted from the linear regression line between ambulatory and casual BPs. Those whose ambulatory BP was higher than predicted had a significantly higher incidence of fatal and non-fatal CV events than those with a lower than predicted ambulatory BP. A second follow-up of 761 patients from the same study group confirmed the usefulness of ambulatory daytime BP as an independent predictor of CV complications when other selected risk factors were statistically controlled (Perloff et al. 1989). Also other studies have confirmed the prognostic value of daytime BP in the prediction of CV events (White et al. 1989, Redon et al. 1998).

6. Blood pressure variability

6.1 Definition and analysis of blood pressure variability

The first observation that BP is not a constant parameter but, on the contrary, that it is highly variable was made in 1733 by Stephen Hales, who performed BP measurements by inserting a glass pipe into the carotid artery of a horse (Mancia et al. 1997a). However, a quantitative analysis to evaluate BP variability over 24 hours in ambulant subjects was made possible only in the late 60s with the development of a technique for monitoring ambulatory intra-

arterial BP in unrestrained individuals. The method has been known as the Oxford method (Bevan et al. 1969, Stott et al. 1976). Since then, BP has been found to fluctuate either spontaneously or in response to a variety of external stimulations also in humans (Mancia et al. 1983a, Turjanmaa et al. 1990, Turjanmaa et al. 1991, Mancia et al. 1992, Parati et al. 1998). Studies have also confirmed that BP variability is unrelated to sex and race (Watson et al. 1980), but increases with age (Zito et al. 1991), and with increasing BP level (Mancia et al. 1983b). It has been suggested that the proper assessment of variability of BP can only be achieved from the analysis of continuous BP recordings (Verdecchia et al. 1999).

More recently, the development of a technique has allowed also non-invasive, continuous monitoring of BP at the finger level both under laboratory conditions (Finapres®) (Imholz et al. 1988, Parati et al. 1989, Imholz et al. 1991) and under ambulatory conditions over 24 hours (Portapres®) (Langewouters et al. 1990, Imholz et al. 1993). The predictive value of ambulatory BPs recorded by those non-invasive devices has not yet been confirmed in longitudinal studies.

6.2 Factors affecting diurnal variation of blood pressure

Ambulatory BP monitoring has shown that BP is characterized by a considerable degree of variability over a 24-hour period. An important source of BP variation is the diurnal change of BP associated with the sleep-awake cycle (Mancia et al. 1983b, Turjanmaa et al. 1987, Pickering 1995). The most significant factors affecting the diurnal change of BP in the published studies have been found to be the definition of day- and night-time, physical activity level at daytime, quality of sleep, body position at night and the position of the cuffed arm relative to the heart at night (Parati 2000). However, the different

definitions among the studies have made the comparison of their results difficult (Parati 2000).

When analysing the daytime and night-time, the methods can be divided into clock-time-independent and clock-time-dependent methods and, on the other hand, into wide methods which use all BP measurements over 24 hours and narrow ones which exclude some of the measurements (Fagard et al. 1997a). Fagard et al. (1997a) have concluded that the asleep and awake BPs, mostly defined as the in-bed and out-of-bed BPs, can be considered the optimum standard. They also suggested that the optimal definition of daytime and night-time BPs is provided by the narrow clock-time-dependent method where data from morning and evening transition periods are excluded.

When assessing the diurnal variation of BP, supine body position at night and the position of the cuffed arm relative to the heart should be taken into account (Parati 2000). Van der Steen et al. (2000) have investigated the influence of four different body positions on BP in 20 normotensive and 20 hypertensive individuals by measuring BP in the back, left side, right side and abdominal positions while simultaneously measuring the distance between the antecubital fossa of the cuffed arm and the sternum. They concluded that both body and arm position can significantly influence ambulatory BP and the day-night difference. In both normotensive and hypertensive individuals, ambulatory SBP and DBP were approximately 4 mmHg higher in the lower arm in the side position compared with the readings in the back position. On the other hand, BPs in the arm above were 15 mmHg lower, on average, than BPs in the back position. The results in the abdominal position did not differ significantly from the readings in the back position. In addition, Cavelaars et al. (2000) have performed 24-hour ambulatory BP monitoring twice in 16 individuals, and used five acceleration sensors mounted on the trunk and legs to quantify the effect of

body position on nocturnal BP. They found that under ambulatory conditions, a highly variable but sometimes substantial number of BP readings at night were taken with the cuffed arm above the heart level. These readings resulted in underestimation of nocturnal BP.

6.3 “Dippers” vs. “non-dippers”

The “dippers”/ ”non-dippers” classification has been first introduced by O´Brien et al. (1988) who reported a higher frequency of stroke in “non-dippers” than in “dippers”. “Dippers” were defined as individuals in whom a reduction in BP was greater from day to night than a given threshold value (10/5 mmHg) and “non-dippers” as individuals in whom the reduction in BP was lesser. The threshold values for classification have been ranged from 10% or 10/5 mmHg to 0% (e.g. no reduction in BP from day to night or a higher BP during the night than during the day) (Verdecchia 2000). Staessen et al. (1997a) have found that the probability of being a “non-dipper” increased 2.8 times from age 30 to 60 years and 5.7 times from age 60 to 80 years, whereas reports from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study have shown that the nocturnal fall in BP is, on average, similar in subjects between ages 25 and 74 years (Mancia et al. 1995, Sega et al. 1997). The nocturnal fall in BP has been suggested, on average, to be preserved in hypertension when comparing hypertensive individuals with normotensives (Belsha et al. 1998). One of the major problems of the classification has been the poor reproducibility of the “dipper” status. The SAMPLE study investigated the phenomenon among hypertensives by repeating ambulatory BP monitoring twice over a period of a couple of months, and found a 40% change in the classification of “dipping” (Mancia et al. 1997, Omboni et al. 1998). Thus, the poor reproducibility of the “dipper” status may weaken it´s usefulness as a risk factor.

6.4 Predictive value of short-term variability of blood pressure

6.4.1 Prediction of blood pressure level and need for antihypertensive medication

Very few studies so far have evaluated the relationship between short-term variability of BP and future BP level. Majahalme et al. (1996a) have found that short-term variability of BP added 3-11% to the predictive power of casual BP on future casual and ambulatory BP after 5 years of follow-up.

6.4.2 Prediction of left ventricular hypertrophy and overall cardiovascular risk

In some cross-sectional studies increased short-term variability of BP has been associated with a higher degree of hypertensive CV complications (Parati et al. 1987, Palatini et al. 1992). However, in those studies LVH has been determined only by electrocardiogram. Schillaci et al. (1998) have investigated the association between short-term variability of BP, assessed with 24-hour noninvasive ambulatory BP monitoring, and LVM at echocardiography in 1822 untreated subjects with essential hypertension. They found that when effects of age, gender, and average 24-hour BP were taken into account, short-term variability of BP was unrelated to LVM. Also other studies have suggested that short-term variability of BP is not significantly related to echocardiographically determined LVM (Majahalme et al. 1996b, Boley et al. 1997).

Few prospective studies have so far investigated the independent significance of BP variability on future CV risk. Frattola et al. (1993) have examined the prognostic value of 24-hour mean BP and short-term variability in 73

hypertensives during a mean of 7.4 years of follow-up by using intra-arterial BP recording. The most important variables as predictors of both LVM and overall target-organ damage at follow-up were casual BP at the follow-up phase, an initial level of end-organ damage and short-term variability of 24-hour BP at baseline. This was the first longitudinal evidence that CV complications of hypertension may depend on the degree of the short-term variability of 24-hour BP. Verdecchia et al. (1996a) have also investigated the relationship between short-term variability of BP, assessed non-invasively, using 24-hour ambulatory BP and subsequent incidence of CV morbid events in hypertensives. They concluded that increased short-term variability of BP at baseline was associated with a higher incidence of CV morbid complications of hypertension, but also with a higher future BP, older age and a higher prevalence of diabetes mellitus. Because of the relevant predictive effect of these associated factors, the adverse prognostic significance of increased short-term variability of BP was no longer detectable in multivariate analysis. Recently, Kikuya et al. (2000) have published the results of a long-term prospective study of ambulatory BP monitoring in Ohasama, Japan concerning 1542 subjects ≥ 40 years of age. They found that BP and HR variabilities, obtained every 30 minutes by ambulatory BP monitoring, were independent predictors for CV mortality in the general population after a mean of 8.5 years of follow-up.

6.5 Predictive value of diurnal variation of blood pressure

Data on whether the diurnal variation of BP is clinically relevant have been controversial. The daytime and night-time BPs have been found to show a close relationship between each other making them to correlate with target-organ damage equally (Mancia and Parati 2000). Thus, it has been suggested that the clinical significance of the phenomenon still needs to be adequately investigated (Mancia and Parati 2000).

6.5.1 Prediction of blood pressure level and need for antihypertensive medication

Only very few studies have investigated the importance of diurnal variation of BP on future BP level. Majahalme et al. (1996a) have reported that diurnal variation of BP did not significantly improve the prediction of future BP level after 5 years of follow-up.

6.5.2 Prediction of left ventricular hypertrophy and overall cardiovascular risk

Some cross-sectional studies have reported that diurnal variation of BP predicts CV damage in hypertension (Verdecchia et al. 1990, Majahalme et al. 1996b, Ferrara et al. 1998, Cuspidi et al. 2001), while others have shown that it does not have any independent role in the development of target-organ damage (Roman et al. 1997, Cuspidi et al. 1999).

A meta-analysis of data of 19 comparative studies involving 1223 participants indicated that night-time BP was not a significantly better predictor of LVM than was daytime BP (Fagard et al. 1995a). Also in the SAMPLE study the regression of LVH was similarly related to treatment-induced changes in daytime and night-time ambulatory BPs (Mancia et al. 1997).

On the other hand, Verdecchia et al. (1994a) have found that CV morbidity was exceedingly high in women with ambulatory hypertension and absent or blunted BP reduction from day to night after an average of 3.2 years of follow-up. The later analysis of a larger study group confirmed that a blunted reduction in BP from day to night predicted an increased CV morbidity in both genders when the “non-dippers” were defined in terms of a night/day ambulatory SBP

ratio > 0.899 for men and > 0.909 for women regardless of the DBP profile (Verdecchia et al. 1997a). Also other prospective studies have suggested that the “non-dipping” status is associated with an increased occurrence of CV events (Zweiker et al. 1994, Staessen et al. 1999), CV mortality (Ohkubo et al. 1997b), all vascular events (Nakano et al. 1998) and a larger number of cerebrovascular events (Yamamoto et al. 1998).

7. White coat hypertension and white coat effect

7.1 Definition of white coat hypertension and white coat effect

The term white coat hypertension (or isolated office hypertension/isolated clinic hypertension) is being used to describe individuals whose BP is persistently elevated in a medical setting and normal in ambulatory BP monitoring (Mancia et al. 1983a, Pickering et al. 1999). The prevalence of the phenomenon has varied from 12.1% to 53.2%, depending on the criteria used to define the upper range of “normal” ambulatory BP (Verdecchia et al. 1992). The originally used criteria were a casual BP that remained above 140/90 mmHg together with a daytime ambulatory BP below 134/90 mmHg (Pickering et al. 1988), but more recently daytime ambulatory BP of 130/80 mmHg (Palatini et al. 1998a), 135/85 mmHg (Owens et al. 1998) or 135/90 mmHg (Hoegholm et al. 1998) has been used to define white coat hypertension. The values of normality of ambulatory BP recommended by the JNC VI (The sixth report of the Joint National Committee 1997) are < 135/85 mmHg when the individual is awake and < 120/75 mmHg when the individual is asleep. It has been suggested that several earlier studies have overemphasized the frequency of white coat

phenomenon, because they have used higher cut-off values dividing ambulatory BP normality and abnormality (Mancia and Parati 2000).

The white coat effect, which is a measure of pressor response to a clinic visit, can be defined operationally as a difference between casual BP and daytime ambulatory BP (Pickering et al. 1999). The white coat effect has been found to be present for the majority of hypertensive individuals (Pickering et al. 1999). It has been suggested to be greater in women than in men (Myers and Reeves 1995), and to persist in patients using antihypertensive medication (Myers 1996).

7.2 Predictive value of white coat hypertension and white coat effect

Data on whether white coat hypertension or white coat effect has predictive value on future hypertension or target-organ damage have been controversial (Mancia and Parati 2000). On the other hand, it has been suggested that when hypertension is in a more advanced stage, organ damage progression or regression depends on 24-hour mean BP values, whereas initially the casual/daytime BP difference may also play a role, possibly because it reflects a BP tendency to vary more markedly in response to inner and outer influences (Mancia and Parati 2000).

7.2.1 Prediction of blood pressure level and need for antihypertensive medication

Bidlingmeyer et al. (1996) have found that 60 of the 81 subjects with white coat hypertension had a mean 12-hour daytime ambulatory BP greater than 140/90 mmHg after 5-6 years of follow-up, suggesting an evolution towards definite hypertension. Thus, they concluded that patients with white coat

hypertension should not be considered as truly normotensives and a careful medical follow-up is warranted. However, later some investigators have suggested that the results can be explained almost entirely by considering the effect of a selection bias; those subjects who had the lowest ambulatory BPs during their first monitoring were expected to have higher ambulatory BPs during their repeated monitoring, while the opposite was expected for casual BPs (Verdecchia et al. 1999).

7.2.2 Prediction of left ventricular hypertrophy and overall cardiovascular risk

Some cross-sectional studies have found that white coat hypertension is associated with increased risk of target-organ damage (Glen et al. 1996, Ferrara et al. 1997, Palatini et al. 1998b, Sega et al. 2001) while others have shown that in comparison with normotensive subjects the white coat hypertensives do not have a greater risk (White et al. 1989, Hoegholm et al. 1993, Cavallini et al. 1995).

To investigate the prognostic significance of white coat hypertension, 1187 hypertensives and 205 healthy normotensives were followed for up to 7.5 years (Verdecchia et al. 1994a). The results showed that CV morbidity was lower in white coat hypertensives than in ambulatory hypertensives and, on the other hand, it did not differ significantly from the CV morbidity rates of normotensives. Khattar et. al (1998) have also found, using intra-arterial ambulatory BP monitoring, that white coat hypertensives had a significantly lower incidence of CV events than mildly hypertensives after 9 years of follow-up.

The prognostic significance of white coat effect has been investigated in the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study including a total of 1522 individuals accounting for 6371 person-years of observation (Verdecchia et al. 1997b). The results showed that the casual-ambulatory BP difference, taken as a measure of the white coat effect, did not predict CV morbidity and mortality in subjects with essential hypertension.

8. Blood pressure responses

8.1 Hypothesis of reactivity

Reactivity can be defined as a deviation of a physiologic response parameter(s) from a comparison or control value that results from an individual´s response to a discrete, environmental stimulus (Matthews 1986). The stimulus can be primarily physical or psychological in nature. The hypothesis of reactivity, in it´s simplest form, then states that individuals who show increased CV reactivity to physically or psychologically stressful stimuli are at increased risk of developing CV disease (Pickering 1991). Two forms of the hypothesis as it relates to hypertension have been proposed; the response to test may correlate with intermittent pressor responses to stress occurring in everyday life and, on the other hand, the stressors may initially produce transient elevations in BP by neurohormonal mechanisms and induce structural changes in arterial wall resulting in a sustained increase in vascular resistance and hence in BP (Pickering 1991).

8.2 Evaluation of reactivity in tests

To examine the role of behavioural factors in the development of hypertension and CV disease, different reactivity tests have been used. The tests have been either predominantly physical, such as dynamic exercise, or predominantly psychological, such as mental arithmetic test. Some have used cold pressor test which includes both of the elements. No consensus has been found as to which test should be used to characterize reactivity, nor how the response should be defined (Pickering et al. 1990, Manuck 1994, Pickering 1996).

Most of the studies have characterized reactivity by measuring BP levels achieved in tests (Dlin et al. 1983, Fixler et al. 1985, Radice et al. 1985, Chaney et al. 1988, Tanji et al. 1989, Wilson et al. 1990, Guerrera et al. 1991, Manolio et al. 1994, Allison et al. 1999, Singh et al. 1999), some have used BP changes from the reference level (Sparrow et al. 1986, Matthews et al. 1993, Everson et al. 1996, Miyai et al. 2000) and few have used both methods (Parker et al. 1987). Different cut-off points have been defined to distinguish individuals with exaggerated BP response to the test (Gottdiener et al. 1990, Lauer et al. 1992, Manolio et al. 1994, Mundal et al. 1996, Allison et al. 1999, Singh et al. 1999), but so far no consensus has been reached regarding the limit of normal BP responses.

The reference BP level has been measured at different time intervals with respect to test; ranging from days or weeks before the test (Everson et al. 1996, Kamarck et al. 2000) to just before the test (Filipovský et al. 1992, Smith et al. 1992, Vriz et al. 1995, Georgiades et al. 1996, Allen et al. 1997, Georgiades et al. 1997, Kop et al. 2000). In addition, no agreement about uniform reference level has been achieved; some have used the sitting position (Filipovský et al. 1992, Georgiades et al. 1996, Everson et al. 1996) and others the supine

(Davidoff et al. 1982, Vriz et al. 1995, Georgiades et al. 1997) or the standing position (Lauer et al. 1992) as a reference level.

In addition, BP level achieved in the test has been defined by different ways; an average of the final minute of the test period (Gottdiener et al. 1990, Lauer et al. 1992, Singh et al. 1999), an average BP level during the whole test period (Georgiades et al. 1996, Allen et al. 1997, Georgiades et al. 1997) or peak BP during the test (Manolio et al. 1994, Mundal et al. 1994, Mundal et al. 1996, Allison et al. 1999, Molina et al. 1999). Most of the studies have focused on measuring SBP (Radice et al. 1985, Sparrow et al. 1986, Tanji et al. 1989, Filipovský et al. 1992, Lauer et al. 1992, Manolio et al. 1994, Allison et al. 1999), some have reported both SBP and DBP (Dlin et al. 1983, Chaney et al. 1988, Wilson et al. 1990, Guerrera et al. 1991, Singh et al. 1999) and few have reported only DBP response (Parker et al. 1987) during a test. It has been suggested that the accuracy of DBP readings may not be high enough by non-invasive methods, because at least during dynamic exercise the noise generated is in the frequency range of Korotkoff sounds, potentially resulting in significant interference with auscultation (Pickering 1987, Tsao et al. 1998).

8.3 Predictive value of blood pressure responses to physical tests

8.3.1 Prediction of blood pressure level and need for antihypertensive medication

Several prospective studies have shown that measurement of BP during dynamic exercise improves the prediction of individuals´ future BP status (Wilson and Meyer 1981, Dlin et al. 1983, Jackson et al. 1983, Guerrera et al. 1991, Miyai et al. 2000), whereas some have suggested that dynamic exercise test BP does not add to the predictive value of casual BP measurements (Fixler

et al. 1985, Majahalme et al. 1997b). In the CARDIA Study, exaggerated SBP response to dynamic exercise was associated with a 2.14 mmHg increase in SBP after 5 years of follow-up among 3741 normotensive young adults (Manolio et al. 1994). Singh et al. (1999) have also found in the Framingham Offspring Study of 1026 men and 1284 women that an exaggerated DBP response to treadmill exercise was an independent predictor of future hypertension. However, a review article by Benbassat and Froom (1986) concluded that the use of exercise testing as a predictor of hypertension still warrants experimental development and confirmation, because 38.1% to 89.3% of those with hypertensive response to exercise did not become hypertensive during a follow-up and, on the other hand, a normotensive response only marginally reduced the risk of future hypertension.

In addition to BPs measured during the dynamic exercise test, some have suggested that even the BP level measured before the test initiation could be a useful predictor of future high BP. Everson et al. (1996) were the first to show that anticipatory BP response to dynamic exercise predicted hypertension or high BP in a group of 508 unmedicated middle-aged men. On the other hand, postexercise BP has also been found to be a useful predictor of future BP status (Davidoff et al. 1982, Tanji et al. 1989, Singh et al. 1999).

Some have found isometric exercise test to be an important predictor of future BP (Parker et al. 1987, Chaney and Eyman 1988, Matthews et al. 1993, Majahalme et al. 1997b), whereas others have concluded that isometric exercise did not significantly contribute to the better prediction of future BP (Fixler et al. 1985). Sparrow et al. (1986) examined the relation of BP taken in sitting, supine and standing positions to subsequent development of hypertension after an average follow-up of 6.6 years among 1564 men. They found that after controlling for sitting levels of BP, supine SBP was a significant predictor of

subsequent hypertension. On the other hand, Parker et al. (1987) concluded that peak DBP response to orthostatic test improves the prediction of future BP levels in children.

8.3.2 Prediction of left ventricular hypertrophy and overall cardiovascular risk

Most of the studies concerning the association between BP responses during physical tests and risk of LVH or overall CV damage have been cross-sectional in nature (Ren et al. 1985, Gottdiener et al. 1990, Michelsen et al. 1990, Schmieder et al. 1990, Taguchi et al. 1990, Fagard et al. 1991a, Lauer et al. 1992, Shimizu et al. 1992, Smith et al. 1992, Trieber et al. 1993, Rostrup et al. 1994, Vriz et al. 1994, Fagard et al. 1995b, Georgiades et al. 1996, Hinderliter et al. 1996, Allen et al. 1997, Majahalme et al. 1997a, Kop et al. 1999, Molina et al. 1999, Kamarck et al. 2000).

Concerning the risk of future LVH, the CARDIA study (Markovitz et al. 1996) examined whether exaggerated BP responses to dynamic exercise or cold pressor test were related to LVM among 3742 young adults after 5 years of follow-up. However, they found that after adjusting for resting BP and other covariates, SBP reactivity to dynamic exercise explained only 3% of the variance in LVM at maximum, and reactivity to cold pressor test explained less than 1%, respectively. On the other hand, Georgiades et al. (1996) have examined the predictive value of tests on future LVM by combining the results of mental arithmetic and isometric stress test in a group of 66 middle-aged borderline hypertensive men. The results showed that the mean BP reactivity in the tests added 15% to the prediction of LVM after 3 years of follow-up. In addition, Kapuku et al. (1999) have investigated the predictive value of tests

among 146 young individuals and found that BP responses to orthostasis did not improve the prediction of future LVM after 2.3 years of follow-up.

Fagard et al. (1991b) have examined among 143 male hypertensives whether BP responses during bicycle ergometry better predict mortality and CV events than casual BP during a follow-up of 1573 patient years. They found that exercise BPs did not add to the prognostic precision when age and BP at rest were taken into account. On the contrary, in the study of 1999 apparently healthy middle-aged men, exercise BP has been suggested to be a stronger predictor than casual BP of CV mortality (Mundal et al. 1994). The later results of the same study group have confirmed that exercise BP was also a stronger predictor than casual BP of morbidity and mortality from myocardial infarction (Mundal et al. 1996). The Normative Aging Study (Sparrow et al. 1984) have investigated the relationship of postural changes in BP to the risk of myocardial infarction among 1359 men after an average follow-up of 8.7 years. The results showed that the relationship of sitting BP to the subsequent incidence of myocardial infarction was modified by a variable formed by subtracting supine DBP from standing DBP. In addition, Allison et al. (1999) have concluded that dynamic exercise BP was a significant predictor of total CV events among 150 healthy, normotensive individuals after a mean follow-up of 7.7 years. In the Paris Prospective Study (Filipovský et al. 1992) CV mortality was also found to be associated with the SBP increase during dynamic exercise test, whereas no association with the resting BP was found among 4907 middle-aged men after an average of 17 years of follow-up.

9. Predictive value of home blood pressure measurements

Home BP measurements have been shown to result in lower BP readings than office measurements and, on the other hand, to correlate more closely with ambulatory BP readings than the office ones (Kleinert et al. 1984, Yarows et al. 2000, Masding et al. 2001). However, there are only little data documenting the validity of home BP for predicting target-organ damage (Yarows et al. 2000).

The importance of home BP and office measurements on electrocardiographic evidence of LVH has been investigated in 50 patients with hypertension during an average of 9 years of follow-up (Ibrahim et al. 1977). The results showed that the reductions in LVH, evaluated as a reduction in maximum precordial QRS voltage, correlated better with home BP than with office measurements. In addition, Jula et al. (1999) have found in a cross-sectional study that self-measured home BPs, when averaged over 4 duplicate measurements, correlated as reliable as ambulatory BP monitoring with echocardiographically determined LVH and albuminuria. On the other hand, Kok et al. (1999) have measured home, ambulatory and office BP of 84 previously untreated hypertensive patients at baseline and after 12 weeks of follow-up. Their findings indicated that home BP was considerably less reproducible than ambulatory BP and did not differ from office BP. In addition, the relationship with LVM appeared to be stronger for ambulatory than for home and office BP. Hozawa et al. (2000) have also performed home BP measurements for 1913 subjects and analyzed their survival status during 8.6 years of follow-up. The results showed that the predictive power of home BP for subsequent mortality was slightly stronger than that of office BP.

10. Heart in hypertension

10.1 Etiology of left ventricular hypertrophy

In humans the heart grows in proportion to body growth in a roughly linear relationship such that the LV weight in grams is three to four times the body weight in kilograms (Lorell and Carabello 2000). During pregnancy, the requirement for an increased blood volume and cardiac output is accompanied by a substantial increase in LVM which regresses over months in the postpartum period (Mesa et al. 1999). In addition, two different morphological types of LV changes have been described in athletes. Concentric hypertrophy occurs in sports with a high isometric component (e.g. weight lifting), and eccentric LVH is found in several sports with isotonic demands (e.g. running) (Pluim et al. 1998). A combination of concentric and eccentric LVH is found in several sports with mixed isometric and isotonic demands (e.g. cycling) (Colan 1997, Pluim et al. 1998).

Although increased arterial BP is usually considered the principal stimulus to hypertensive cardiac hypertrophy, only a relatively modest percentage of the observed variance in LVM has been accounted by BP (Korner and Jennings 1998, Benjamin and Levy 1999). It has been estimated that no more than 25-35% of variability of LVM can be predicted by the level of BP (Devereux et al. 1993a). It has also been suggested that the effect of BP is a 4-7% change in LVM per 10 mmHg change in SBP (Korner and Jennings 1998).

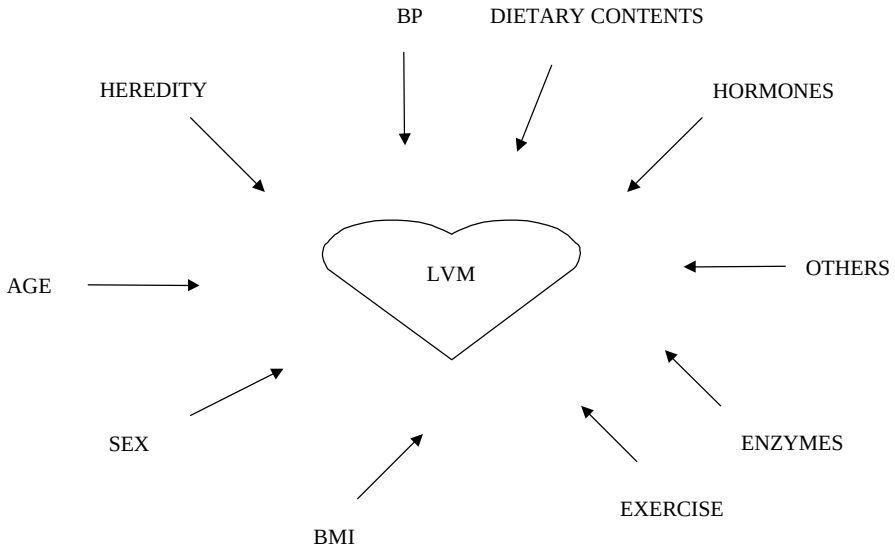
Concerning demographic variables, men have been found to have greater LVM after puberty than women, even after differences in body size have been considered (Shub et al. 1994, Gardin et al. 1995, Muiesan et al. 1996a, Schirmer

et al. 1999). This difference has been shown to parallel the sex difference in lean body mass reflecting genetic, hormonal, or exercise effects that influence both skeletal and heart muscle (Devereux and Roman 1999). Some have also suggested that LVM increases monotonically with age (Levy et al. 1988), whereas others have indicated that LVM may remain relatively stable with age in the absence of other risk factors (Dannenberg et al. 1989). Thus, an increase of LVM might not be an obligatory part of aging, but rather a reflection of increasing prevalence of CV conditions associated with aging. In addition, LVM has been reported to be significantly higher in blacks than in whites, even after adjustment for other covariates (Gardin et al. 1995). There is also some evidence that heredity explains a small proportion of the variance in LVM (Bielen et al. 1990, Harshfield et al. 1990, Bielen et al. 1991, Verhaaren et al. 1991, Schunkert et al. 1999). In the Framingham Heart Study the heritable contribution to variance of LVM was 2-3% (Post et al. 1997).

Numerous studies have shown that obesity is associated with increased LVM (Messerli et al. 1983, Daniels et al. 1990, Savage et al. 1990, Lauer et al. 1991, Liebson et al. 1993, de Simone et al. 1994, Schirmer et al. 1999, Garner et al. 2000). In the Framingham Population obesity was independently predictive of risk of LVH in both sexes, with an odds ratio of 1.47 in men and 1.51 in women for every 2 kg/m² increment in BMI (Levy et al. 1988). The effect of obesity on cardiac anatomy has been found to be greater in women than in men also in other studies (de Simone et al. 1994). On the other hand, Bella et al. (1998) have reported that increased LVM in overweight individuals is more strongly related to their fat-free mass than to adipose mass, waist/hip ratio or BMI. Several reports have also shown a link between salt intake and LV growth in hypertensive patients (Schmieder et al. 1988, du Cailar et al. 1989, Daniels et al. 1990, Liebson et al. 1993). Increasing LVM has also been found to associate with a wide variety of other variables, including excess in alcohol intake

(Manolio et al. 1991), smoking (Gardin et al. 1997), diabetes (Kuperstein et al. 2001), insulin resistance (Marcus et al. 1994), growth hormone and growth factors (Lim et al. 1992), angiotensin II (Sadoshima et al. 1993), polymorphism of the angiotensin converting enzyme (ACE) gene (Gharavi et al. 1996), plasma renin activity (Bauwens et al. 1991), noradrenaline (Trimarco et al. 1985), blood viscosity (Devereux et al. 1984) and aldosterone (Bauwens et al. 1991, Weber et al. 1991). However, about 50-75% of the variance of LVM remains unexplained by variables that are currently assessed (Benjamin and Levy 1999).

Figure 1. Factors affecting LVM



10.2 Evaluation of left ventricular hypertrophy

10.2.1 Prevalence of left ventricular hypertrophy - electrocardiography vs. echocardiography

In the Framingham Heart Study population the prevalence of LVH on the electrocardiography (ECG) was only 2.9% in men and 1.5% in women (Kannel et al. 1969a). However, in the same population the prevalence of echocardiographic LVH was 16% in men and 19% in women (Levy et al. 1988). When further comparing the ECG and echocardiography in 4684 Framingham Study individuals on diagnosing LVH, the overall sensitivity of the ECG on diagnosis of LVH was only 6.9%, whereas the specificity was 98.8% (Levy et al. 1990b).

The prevalence of LVH in hypertension has been found to be highly dependent on the population being studied (Devereux et al. 1987). In a population-based sample of 3287 subjects aged 25-85 years, the prevalences of LVH were 14.9% in men and 9.1% in women (Schirmer et al. 1999). On the other hand, LVH has been detected in 12 to 23% of mildly hypertensive patients (Hammond et al. 1986, Liebson et al. 1993, Liebson et al. 1995, Armario et al. 1999), in 50% of mild-to-moderately hypertensive patients (Savage et al. 1979), and even almost in 90% of hospitalized patients (Devereux et al. 1987).

10.2.2 Left ventricular mass and geometry defined by echocardiography

M-mode echocardiography is the most widely used, anatomically validated method of determining LVM (Devereux and Reichek 1977). Two geometric formulas have been used to calculate LVM. The Penn convention ($1.04\ [(IVST + LPWT + LVEDD)^3 - LVEDD^3] - 13.6g$) excludes endocardial

and epicardial surfaces in the measurement of wall thickness and includes endocardial surfaces in the LV dimension measurement (Devereux and Reichek 1977). Comparable LVM values can be obtained with measurements made according to the American Society of Echocardiography convention (ASE) using the formula: 0.8 (ASE mass) + 0.6 g (Devereux et al. 1986).

No uniform method has been available for indexing LVM by body size or composition. LVH has been identified by calculation of LVM that has been indexed by body surface area (BSA) (Verdecchia et al. 1996b, Armario et al. 1999), $BSA^{1.5}$ (de Simone et al. 1992), height (Lauer et al. 1991, Schirmer et al. 1999), $height^{2.0}$ (Lauer et al. 1994), $height^{2.13}$ (de Simone et al. 1992, de Simone et al. 1994), $height^{2.7}$ (de Simone et al. 1992) or $height^{3.0}$ (Daniels et al. 1995). BSA has been calculated by the Du Bois formula (Du Bois and Du Bois 1916). Some have also suggested that LVM is more strongly related to fat-free than to adipose mass, and that indexing LVM by fat-free mass may increase the sensitivity to detect LVH (Bella et al. 1998, Whalley et al. 1999).

Thus, considerable controversy has been existed regarding the optimal method for indexing LVM to body size until Liao et al. (1997) compared the impact of various methods of indexation on mortality after a mean of 7 years of follow-up among 988 hospitalized patients. The results confirmed that because of the high correlation among various body size indexes, LVH, defined by different indexes for LVM, similarly confered an increased risk of mortality in patients with or without CHD. Wachtell et al. (2000) has also recently concluded that various methods of indexing LVM and calculating relative wall thickness (RWT) resulted in a similar risk of CHD.

Another controversy has existed concerning the partition values for defining LVH. The most commonly used methods have been to distinguish the LVH by

using sex-specific 95th (de Simone et al. 1994, Gharavi et al. 1996) or 97th (Devereux et al. 1987) percentiles for LVM. Some have defined LVH as a LVM 2 standard deviations (SDs) or more above the mean for previously defined healthy non-obese reference group (Levy et al. 1990, Lauer et al. 1991). LVM is also commonly analysed as a continuous variable underlining the artificiality of specific partition lines (Bauwens et al. 1991, Marcus et al. 1994).

In addition to LVM, echocardiography has allowed the establishment of LV geometry. In hypertensive patients different types of LV changes have been distinguished. In concentric LV remodelling LVM is normal and RWT is increased. In concentric LVH, both LVM and RWT are increased, whereas in eccentric LVH, LVM is increased and RWT is normal. RWT has been calculated as either 2 x LPWT/LVEDD (RWTa) (Reichek and Devereux 1982) or as (IVST + LPWT)/LVEDD (RWTb) (Verdecchia et al. 1994b). It has been estimated that increased RWT is present when the ratio of RWTa exceeds 0.43, which represents the 97.5th percentile in normal subjects (Roman et al. 1995) or when RWTb exceeds 0.45, which represents the 96th percentile in normal subjects (Wachtell et al. 2000). In addition, LVH may be symmetric or, on the other hand, asymmetric when LVH occurs predominantly on the septum (Gosse and Dallocchio 1993).

10.3. Predictive value of left ventricular hypertrophy

10.3.1 Echocardiographically determined increased left ventricular mass

LVH can be considered as a manifestation of pre-clinical disease, which may be associated with an absence of symptoms for many years before the development of clinic cardiac disease (Frohlich 1999, Lorell and Carabello 2000). Increased LVM has been shown to be a powerful predictor of CV morbidity and mortality

(Casale et al. 1986, Cooper et al. 1990, Koren et al. 1991, Verdecchia et al. 1996b, de Simone et al. 2001). The Framingham Heart Study has shown a direct and progressive relationship between LVM and CV risk (Levy et al. 1990a). During 4 years of follow-up, each 50 g/m increase in LVM in men was associated with a 1.49-fold increase in relative risk of CHD, a 1.73-fold increase in relative risk of death from CHD, and a 1.49-fold increase in relative risk of death from all causes. Schillaci et al. (2000) have also found that the powerful relation between LVM and risk of CHD in subjects with uncomplicated essential hypertension was continuous over a wide range of LVM values, even below the current ”upper normal” limits. In addition, in the study of 3661 subjects from the Framingham population, increased LVM was associated with an increased risk of sudden death after accounting for other known risk factors (Haider et al. 1998). On the other hand, de Simone et al. (2001) have found recently that hypertensive patients with levels of LVM lower than needed to compensate cardiac workload exhibited hyperdynamic circulatory status and the same risk pattern as patients with higher values of LVM, possibly due to activation of the sympathetic system.

10.3.2 Echocardiographically determined left ventricular geometry

Some reports have indicated that assessment of LV geometry, on the basis of LVM and RWT, improves the predictive value of LVM on prognosis (Koren et al. 1991a, Ghali et al. 1998). In those studies concentric and eccentric types of hypertrophy have been associated with a higher incidence of morbid events and a worse CV outcome than normal geometry or concentric remodelling. Verdecchia et al. (1995a) have also confirmed the adverse prognostic significance of concentric remodelling in 694 hypertensive patients without LVH. The incidence of CV morbid events was 2.39 per 100 patient-years in those with concentric remodelling and 1.12 in those with normal geometry.

In addition, an isolated relative increase in the septal thickness of the LV has been reported to associate with an increased CV risk (Verdecchia et al. 1994b).

On the contrary, the Framingham Heart Study did not support the independent role of LV geometry (Krumholz et al. 1995). The association between the type of geometry and prognosis was largely attenuated after adjustment for LVM. Some other reports have also suggested that LV geometry did not have an additional predictive value over LVM (Verdecchia et al. 1996b).

10.4 Reversal of left ventricular hypertrophy

10.4.1 Reversal of left ventricular hypertrophy by non-pharmacological treatment

MacMahon et al. (1986) have shown that weight reduction was directly associated with reduced LVM in 41 overweight hypertensive patients, independent of changes in BP. At the end of a 21-week follow-up period, patients had lost 8.3 kg, on average, and their LVM was decreased by 16% when adjusted for BSA. In the Treatment of Mild Hypertension Study (TOMHS), nutritional-hygienic intervention, with emphasis on weight loss and reduction of dietary sodium, was as effective in decreasing LVM as combinations of nutritional-hygienic therapy and low-dose antihypertensive monotherapy (Liebson et al. 1995). Also other reports have indicated that sodium restriction decreases LVH (Ferrara et al. 1984, Jula and Karanko 1994).

10.4.2 Reversal of left ventricular hypertrophy by antihypertensive medication

Reports of the Framingham Heart Study from 1950 to 1989 have suggested that increasing use of antihypertensive medication has resulted in a reduced prevalence of high BP and a concomitant decline in LVH in the general population (Mosterd et al. 1999). The meta-analysis of 109 treatment studies concluded that after an average of 10.1 months of follow-up, LVM was reduced by 11.9%, in parallel with a reduction of MAP by 14.9% (Dahlöf et al. 1992). When comparing different antihypertensive therapies, ACE inhibitors reduced LVM by 15%, diuretics by 11.3%, calcium antagonists by 8.5% and ß-blockers by 8%. Schmieder et al. (1996) have also published a meta-analysis of 39 randomized double-blind studies and found that the ACE inhibitors were more potent than calcium antagonists, ß-blockers or diuretics in the reduction of LVM after a mean of 25 weeks of antihypertensive therapy. In the most recent meta-analysis of the same group, overall LVM was the more reduced the greater the decrease in SBP, the longer the duration of therapy and the higher the pretreatment value of LVM (Schmieder et al. 1998). LVM decreased by 12% with ACE inhibitors, 11% with calcium antagonists, 8% with diuretics and 5% with ß-blockers. On the other hand, the Veterans Affairs Cooperative Study Group has found that patients with adequate BP control on captopril, hydrochlorothiazide or atenolol showed a reduction of LVM after 1 year of treatment, whereas patients with diltiazem, clonidine or prazosin did not (Gottdiener et al. 1997). In addition, Schlaich and Schmieder (1998) have reported in a meta-analysis of double-blind, randomised, controlled clinical studies published until the end of 1996 that ACE inhibitors and calcium antagonists were more potent than ß-blockers in their ability to reduce LVH, with diuretics in the intermediate range.

10.4.3 Predictive value of reversal of left ventricular hypertrophy

To date only few studies have examined the potential clinical prognostic benefit obtained from regression of LVH (Yurenev et al. 1992, Agabiti-Rosei and Muiesan 1998). The Framingham Heart Study has shown that ECG evidence of reversal of LVH in 524 participants was associated with a decreased risk of CHD after an average of 5 years of follow-up (Levy et al. 1994). On the other hand, Koren et al. (1991b) have found, using echocardiography, a higher risk of subsequent CV events in those in whom LVH persisted or developed despite treatment than in those in whom LVM remained normal or decreased during 5.5 years of follow-up. A 10-year follow-up of 151 patients with uncomplicated hypertension also showed that the cumulative incidence of non-fatal CV events was significantly higher in the group of patients without regression of LVH (Muiesan et al. 1995, Muiesan et al. 1996b). In addition, Verdecchia et al. (1998a) have concluded that a serial reduction in LVM in uncomplicated subjects with antihypertensive medication has a favourable prognostic value by predicting a lesser risk of subsequent CHD among 430 hypertensive patients. In the near future the results of the Losartan Intervention For Endpoint (LIFE) study may provide us new insights concerning the relation between antihypertensive medication and CV complications in patients with essential hypertension and LVH (Kjeldsen et al. 2000).

AIMS OF THE STUDY

The aims of the present study were:

1. To examine the role of casual BP measurements and ambulatory 24-hour BP levels and variability in the prediction of future BP level, need for antihypertensive medication and LVM.
2. To clarify the importance of BP responses to tests as predictors of future BP level, need for antihypertensive medication and LVM.

The specific questions were:

1. Are future SBP and DBP levels as predictable and, on the other hand, are the baseline SBP and DBP levels as good in predicting future BP level, need for antihypertensive medication and LVM?
2. What is the predictive value of BP responses to independent postural and exercise tests on future BP level, need for antihypertensive medication and LVM?
3. What is the predictive value of different BP components (SBP, DBP and PP) on future LVM?
4. What is the significance of baseline LVM measurements in predicting LVM after 10 years?

SUBJECTS AND METHODS

1. Subjects

The participants in the Studies **I-IV** were healthy male volunteers recruited from a routine health check-up offered to all 35-, 40- and 45-year-old subjects at the Community Health Care Centre of the City of Tampere from 1987 to 1991. Out of 16 059 eligible men, 74% participated in the health check-up. Healthy subjects who were taking no medication, were informed about the BP study by a health care nurse. Those showing interest were interviewed by phone and, if volunteered, appointments were scheduled. At baseline, a comparable number of unmedicated participants with different BP status (normotensive, NT; borderline hypertensive, BHT and mildly hypertensive, HT) was tried to be included in the study. Using World Health Organization criteria (WHO Expert Committee 1978), the subjects were classified based on repeated casual BP measurements obtained during 2 months before the trial. At baseline, 34 of the subjects were NT (SBP ≤ 140 mmHg and DBP ≤ 90 mmHg), 29 were BHT (SBP 141-159 and/or DBP 91-94 mmHg) and 34 were HT (SBP ≥ 160 and/or DBP ≥ 95 mmHg). Physical examination, haematological and biochemical screening tests, chest X-ray and ECG were normal in the whole study group.

At baseline, the participants were given thorough information of the results of the tests by the authors. They were also given a written summary of the results for a primary care physician to take them into consideration in the clinical decision making. The participants were requested to contact immediately their primary care physicians, whose treatment decisions determined the quality of

the treatment. The participants were allowed to make their own choice concerning the primary care physician.

The 10-year follow-up phase was started in December, 1998 and completed in December, 1999. After a mean of 10.8 years (range 8.8 to 12.3) of follow-up, complete follow-up data was obtained for Studies **I** and **II** from 87 (90%) subjects and for Studies **III** and **IV** from 86 (89%) subjects. The personal characteristics of the subjects at baseline in Studies **I-IV** are presented in Table 1. The BP values of the subjects at baseline in Studies **I-IV** are presented in Table 2. The subjects who did not participate in the follow-up phase were distributed equally to each original BP group. There were three originally NT, three originally BHT and four originally HT subjects. The population registry confirmed that none of them had died. Two of them refused to participate in the follow-up phase for personal reasons, and eight subjects did not answer the invitation letter. Many of them had moved to another town, and one had moved abroad.

Table 1. Personal characteristics of the subjects at baseline in Studies I-IV.

Study	Subjects (n)	Age (years)	BMI (kg/m²)	Smoking (%)	Exercise (h/week)	Family history of HT in father (%)	Family history of HT in mother (%)
I-II	87	40 (4.2)	26 (2.8)	39	1 (1-12)	49	51
III-IV	86	40 (4.0)	26 (2.8)	38	1 (1-12)	49	51

Numbers of persons, means (SD) and medians (range) are given. N, number; BMI, body mass index; h, hour; HT, hypertension.

Table 2. BP values of the subjects at baseline in Studies I-IV.

Study	Subjects (n)	Casual SBP (mmHg)	Casual DBP (mmHg)	Casual PP (mmHg)	IAMB 24h SBP (mmHg)	IAMB 24h DBP (mmHg)	IAMB 24h PP (mmHg)
I-II	87	143 (13.6)	89 (10.4)	-	126 (11.3)	76 (7.1)	-
III-IV	86	143 (13.7)	89 (10.4)	54 (10.4)	125 (11.0)	75 (7.1)	50 (6.5)

Means (SD) are given. In Studies **I** and **II** the PP values were not included in the analyses. N, number; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; IAMB, intra-arterial ambulatory blood pressure.

2. Study protocol and ethical aspects

At baseline

Casual BP measurements, 24-hour intra-arterial ambulatory BP monitoring, psychological tests, physical tests and echocardiography.

At follow-up

Casual BP measurements, 24-hour non-invasive ambulatory BP monitoring and echocardiography.

The study protocol was approved by the Ethics Committee of Tampere University Hospital, and a written informed consent was obtained before the baseline and follow-up studies.

3. Methods

3.1 Casual blood pressure measurements

At baseline

Casual BP was measured using the standard cuff method on two or three occasions during the 2-month period before the study. In each session, three different readings, each at least one minute apart, were taken. On the first occasion the measurements were made by the same experienced nurse and other measurements by the same physician who also took the history and performed a complete physical exam. All the readings were taken in a sitting position after at least 10 minutes of rest. SBP was read at the first Korotkoff sound and DBP at the disappearance of the Korotkoff sounds (phase V). The deflation rate was 2 mmHg/s. The mean of all the measurements was used for comparisons.

At follow-up

At follow-up, casual BP was measured in a sitting position after 10 minutes of rest using a calibrated aneroid barometer (Speidel and Keller®) and the same technique as at baseline. All the measurements were made by the same experienced nurse. Casual BP was recorded on two consecutive days, before the ambulatory recording (three measurements at least 1 minute apart) and after it (two measurements at least 1 minute apart). The average of the five readings was used for the analyses.

3.2 Ambulatory blood pressure measurements

At baseline

Ambulatory BP was recorded intra-arterially for 24 hours by the Oxford technique (Bevan et al. 1969, Stott et al. 1976, Kalli et al. 1985) in the brachial artery of the non-dominant arm. The signals were collected on Medilog 20 FM recorders (Oxford Medical Systems Ltd, Abingdon, Oxford, UK). The signal analysis system used in the present study has been described and validated in the previous studies (Kalli et al. 1985, Kalli 1987, Turjanmaa 1989). After signal processing, the average 30-second BP was used for the calculations. The average systolic and diastolic BP and PP were computed for the whole 24-hour period and also for daytime (8:30 AM to 1:30 PM) and night-time (0:30 AM to 5:30 AM) subperiods. The variability was analysed by using the cumulative distribution curve. The 80% range of variability (RV80) measurements were calculated as an index of BP variability for each BP period considered. The RV80 was the difference between the 90^{th} and 10^{th} percentiles of the cumulative distribution curve. By using RV80 values the effect of extreme BP values (low or high) was eliminated (Turjanmaa et al. 1991). The subjects were asked to follow their usual daily routines and to keep a diary. Most of the subjects went to work during the daytime period. It was checked from the diaries that the subjects stayed in bed during the night-time period.

At follow-up

Ambulatory BP monitoring was performed with the previously validated (O´Brien et al. 1991a, O´Brien et al. 1991b) DIASYS 200 device (Novacor SA®). BP was measured at 15-minute intervals between 6:00 AM and 10:00 PM, and at 30-minute intervals between 10:00 PM and 6:00 AM. 24-hour BP was calculated using hourly means. Only recordings with less than 10% missing or inappropriate values were accepted. The raw data were checked

manually and inappropriate readings (Devereux et al. 1993b) were removed. The subjects were asked to follow their usual daily routines and to keep a diary. Most of the subjects went to work during the daytime period. From the diaries it was ensured that the subjects stayed in bed during the night-time period.

3.3 Psychological and physical tests

The psychological and physical tests were initiated at the same time in the morning for each of the subjects. Guidance of recommended breakfast was provided to all of them. Alcohol was not allowed during the intra-arterial ambulatory BP monitoring (IAMB) period or two days before it. Alcohol, smoking and caffeine were neither allowed during the test period. Smoking was allowed during the ambulatory recording period, and the time of smoking, as well as other events were entered in detail in the diary (Tuomisto 1995).

The tests were performed during the first six hours of intra-arterial BP recording. Psychological tests, which were not included in this thesis, were done first. The other tests were performed always in the same order. The temperature of the study room was standardized and the same nurse and physician were present during the whole test series.

Postural tests

Both of the first two postural tests, sitting and supine, lasted for 10 minutes. The subjects were awake, but not allowed to speak during the tests. Standing was the third postural test, lasting for 9 minutes. During the standing test, subjects were asked to stand comfortably without moving or speaking. The time of the tests was marked on the BP signal tape with a special event marker prepared for these purposes (Kalli 1984, Turjanmaa et al. 1991) and double-checked with a

clock. The mean intra-arterial BP of the final minute of each test was used to evaluate the effect of each position on the BP.

Isometric exercise test

A hand-grip test was used as an isometric exercise. The subjects squeezed a Vigorimeter (Martin®) at 30% of their maximal effort, which was defined as a mean of three maximal contractions performed one day before the test period. They gripped as long as they could or 5 minutes at the most. The Valsalva phenomenon was prevented by talking with the subject during the test. The mean intra-arterial BP during the final minute of the test was used for comparisons.

Dynamic exercise test

Dynamic exercise was performed in an upright position using a bicycle ergometer (Siemens Elema®). The starting work load was 50 W, and the work load was increased in a stepwise manner with increments of 50 W/4 minutes until 85% of the age-specific maximum HR was reached. The age-specific maximum HR was defined by the formula: 205 – subject´s age (years)/2. The pedalling frequency was 60 r/min. The mean values of intra-arterial BP during the final minute of the pre-exercise period (the subject sitting on the bicycle ergometer before test initiation), the second work load, the final work load and 10 minutes after the exercise test were used for comparisons.

Both the BP level achieved in tests and the BP change from the reference level were analysed. The mean intra-arterial BP of the final minute of the sitting test was taken as the reference BP level.

Table 3. Protocol of the study at baseline

Data acquisition:

Ambulatory 24-hour recording:	**Tests:**
- continuous BP recording	- psychological tests
- ECG	- sitting
- events	- isometric exercise
- time of day	- supine
	- standing
	- dynamic exercise

Data analysis:

Ambulatory 24-hour recording:

- calculation of mean HR, mean BP (SBP, DBP, PP) and RV80 for
  - -24 hours
  - -evening period (04.30 – 09.30 PM)
  - -night period (00.30 – 05.30 AM)
  - -day period (08.30 AM – 01.30 PM)

BP responses to tests:

- achieved HR and BP (SBP, DBP, PP) levels during the tests and BP changes from the reference level (sitting)

3.4 Echocardiography

All the echocardiographic studies both at baseline and at follow-up were performed by the same cardiologist who was unaware of the subjects´ BP and clinical status. The subjects were studied in a partial left lateral decubitus position with 2.5 MHz transducer placement in the third to the fifth intercostal space. M-mode echocardiograms were made under two-dimensional control using standard techniques and commercially available machines: at baseline with a Toshiba (SSH-65A®) and at 10-year follow-up with a Vingmed System Five (FA000710®). LV values obtained from an average of at least four

consecutive cardiac cycles were used for calculations. LVM measurements and calculations were made using the Devereux formula and Penn convention (Devereux and Reichek 1977): LVM (g) = 1.04 x [(LVEDD + IVST + LVPWT)^3 - LVEDD^3] – 13.6g where LVEDD is the LV internal dimension at end-diastole, IVST the interventricular septal thickness at end-diastole and LVPWT the LV posterior wall thickness at end-diastole. LVM index (LVMI) (g/m^2) was calculated using the equation LVM/BSA. The LVMI values were used in the analyses as continuous variables. BSA (m^2) was calculated using the Du Bois Formula (Du Bois and Du Bois 1916). RWT was calculated as (IVST + LVPWT)/LVEDD and fractional shortening [FS(%)] as [(LVEDD – LVESD)/LVEDD] x 100 where LVESD is LV internal dimension at end-systole.

At baseline, the inter-observer agreement was assessed by examining 12 randomly selected men from the study sample (two separate echo registrations) blindly by two cardiologists (the cardiologist who made the echocardiography studies in this study and another cardiologist). The calculations of limits of agreement were performed according to the principles recommended by Bland and Altman (1986). The following differences (coefficient of repeatability) were found: IVST 0.56 mm (1.90), LVPWT 0.36 mm (1.15) and LVM 5.8g (22.78).

3.5 Statistical methods

Analysis of variance (ANOVA) was used to compare the original BP groups with respect to continuous variables and the Kruskal-Wallis test for non-normal variables. The paired t-test and Wilcoxon´s matched pairs test were used to test the within-group changes of the continuous and ordinal variables, respectively. The Chi-square test and the Armitage trend test were used to test the differences between proportions. The McNemar test was used to indicate within-group

changes in proportions. Stepwise regression analyses were performed to predict the level of casual and ambulatory BP, and LVMI after 10 years of follow-up. Stepwise regression analyses were also performed to predict the change of LVMI during the follow-up. Adjusted coefficients of determination (adj.R^2) were calculated to compare the predictive value of casual and ambulatory BP and BP responses to tests on future BP level and LVMI. Stepwise logistic regression analyses were performed to predict the future need for antihypertensive medication. Cox and Snell R^2 statistics were calculated to indicate the explained proportion in the logistic model. The probabilities of future medication were estimated for each subject using the three final logistic regression models. To compare the three logistic models and to detect the best cut-off point in predicting the future need for BP medication, receiver operator characteristic curves (ROC) were constructed graphically by plotting the sensitivity against 100-specificity for several cut-off points. The data were analysed using the SPSS statistical package (Versions 9.0 and 10.0; SPSS Inc., Chicago, Illinois, USA). The statistical methods used have been described in detail in the original publications.

RESULTS

The final prediction models have been described in detail in the original publications (**I-IV**). The condensed tables (Tables 4-6), which are included into this results section (pp.73-75) show the predictive value of casual BP, ambulatory BP and BP responses. The tables of the original publications (**I-IV**) show also the different BP components in the final prediction models. In the results section the tables of the original publications (**I-IV**) have been used as

references. The condensed tables have been made to facilitate the comparison of the predictive value of casual BP, ambulatory BP and BP responses.

1. Prediction of future blood pressure level

1.1 Demographic variables at baseline and their change during the follow-up

The results concern the 87 (90%) subjects who were eligible for both the baseline and 10-year follow-up phases. At baseline the demographic and anthropometric variables did not differ significantly between the original BP groups (**I**: Table 1). During the follow-up, body weight increased significantly in the whole study group ($p<0.0001$), whereas no significant differences in body weight increase were found between the original BP groups (ANOVA, $p=0.42$). The mean change in BMI during the follow-up was +1.6 kg/m² (95% CI 1.1 to 2.1), while no significant differences were observed between the original BP groups (ANOVA $p=0.79$). The proportion of smokers increased significantly from 34/87 (39%) to 44/87 (51%) men (McNemar test $p=0.02$). Also the amount of exercise increased significantly in the whole group, the average increase being 2 hours per week ($p<0.0001$), while there were no significant differences between the original BP groups (Kruskal-Wallis test $p=0.92$).

1.2 Change in blood pressure classification during the follow-up

The original BP classification deteriorated during the follow-up in 35 cases (40%), whereas it improved in six cases (7%) (McNemar test $p<0.0001$) (**I**: Table 2). When analysing the original BP groups, 77% of the BHT group

became hypertensive, 48% of the NT group changed BP class and 43% of originally hypertensives were initiated antihypertensive medication. Of the personal characteristics included in the analysis, only the amount of exercise tended to protect from BP elevation. The BP classification deteriorated in 41% of the subjects who exercised more than two hours per week compared with 67% of the subjects who did only one hour exercise per week (p=0.08).

1.3 Predictive value of ambulatory vs. casual blood pressure

The analyses included only subjects (n=67) without antihypertensive medication. The predictive value of intra-arterial ambulatory 24-hour, daytime and night-time BPs was compared with that of casual BP in predicting future casual and 24-hour ambulatory BP (**I**).

The results showed that ambulatory BP, especially 24-hour BP, improved the prediction of future BP level compared with casual BP measurements (**I**: Tables 3 and 4). Future SBP level was also more predictable than DBP level. Thus, the 24-hour mean SBP was the best predictor of future casual SBP (adj.R^2=0.420, vs. casual SBP as a predictor adj.R^2=0.356), and the 24-hour mean DBP was the best predictor of future casual DBP (adj.R^2=0.301, vs. casual BP as a predictor adj.R^2=0.259). The analyses also showed that the predictive value of baseline casual DBP on future casual DBP was so weak that also casual SBP was included in the final prediction model, whereas the other models concerning the prediction of future SBP or DBP level included only SBP or DBP as a final predictor variable. The 24-hour mean SBP was best predicted by baseline 24-hour SBP (adj.R^2=0.540, vs. casual SBP as a predictor adj.R^2=0.275), and the 24-hour mean DBP was best predicted by baseline 24-hour DBP (adj.R^2=0.292, vs. casual DBP as a predictor adj.R^2=0.214). The subjects´ personal characteristics (age, weight, BMI, smoking, family history of hypertension in

mother or father) did not improve the predictive value of baseline BPs on future BP level.

1.4 Predictive value of blood pressure responses vs. casual blood pressure

The analyses included only subjects (n=67) without antihypertensive medication. The predictive value of BP responses to postural and exercise tests was compared with that of casual BP in the prediction of future casual and 24-hour ambulatory BP (**II**).

When predicting future BP level, BP responses to tests were found to improve the predictive value of casual BP readings (**II**: Tables 2 and 3). The prediction of casual SBP was best improved by SBP at 10 minutes after the dynamic exercise test (adj.R^2=0.448, vs. casual SBP alone adj.R^2=0.356), and the prediction of casual DBP was improved most by DBP at 10 minutes after the dynamic exercise test (adj.R^2=0.282, vs. casual BP alone adj.R^2=0.259). SBP in the supine test best improved the prediction of 24-hour SBP (adj.R^2=0.448, vs. casual SBP alone adj.R^2=0.275), and DBP in the standing test best improved the prediction of 24-hour DBP (adj.R^2=0.252, vs. casual DBP alone adj.R^2=0.214). When analysing the test BPs, only the BPs achieved during the tests, but not the BP changes from the reference level, improved the predictive value of the casual BP measurements. The subject´s personal characteristics and the duration of the dynamic exercise test did not improve the predictive value of baseline BPs on future BP level.

2. Prediction of future need for antihypertensive medication

At follow-up phase, 20/87 (23%) of the subjects had antihypertensive medication. Nine of them (45%) were using monotherapy, eight (40%) subjects a combination of two drugs and three (15%) subjects a combination of three drugs. The monotherapies were: ß-blocker (five), ACE inhibitor (one) and calcium antagonist (three). The combinations of two medicines were: ß-blocker + diuretic (two), ACE inhibitor + diuretic (one), ß-blocker + calcium antagonist (three) and ACE inhibitor + calcium antagonist (two). The combinations of three medicines were: ß-blocker + ACE inhibitor + diuretic (one) and ACE inhibitor + calcium antagonist + diuretic (two). Compared with the NT group, the BHT group had a ninefold risk (p=0.049, OR=9.0) and the HT group a 23-fold risk (p=0.004, OR=22.9) of having antihypertensive medication at follow-up.

2.1 Predictive value of ambulatory vs. casual blood pressure

The analyses included all the subjects (n=87). The predictive value of intra-arterial ambulatory 24-hour, daytime and night-time BPs was compared with that of casual BP in predicting future need for antihypertensive medication (**I**).

The results showed that the predictive value of ambulatory BP on future need for antihypertensive medication (Cox-Snell R^2=0.399) was better than casual measurements only (Cox-Snell R^2=0.164) (**I**: Table 5). Each of the final prediction models concerning ambulatory BP included at least one BP variability parameter (RV80) showing that BP variability truly improved the prognostic value of mean BP on future need for antihypertensive medication. Indeed, the best prediction model included three BP variability parameters

(RV80) and only one BP mean parameter. The predictive effect of the BP variables was again so strong that the personal characteristics did not enter into any final prediction model.

2.2 Predictive value of blood pressure responses vs. casual blood pressure

The analyses included all the subjects (n=87). The predictive value of BP responses to postural and exercise tests was compared with that of casual BP in predicting future need for antihypertensive medication (**II**).

The analyses showed that the BP levels achieved during the tests improved the predictive value of casual BP measurements, while the BP changes from the reference level, duration of dynamic exercise or subjects´ personal characteristics did not improve the prediction of future need for antihypertensive medication (**II**: Table 4). The best predictor model included, in addition to casual SBP, DBP during the final minute of the pre-exercise period (Cox-Snell R^2=0.256 vs. casual SBP alone, Cox-Snell R^2=0.164). Also the DBPs achieved in the postural tests, at the isometric exercise and at the dynamic exercise work load 2 improved the prediction of future need for antihypertensive medication.

3. Prediction of left ventricular mass

When analysing the 86 subjects on whom the echocardiography data was available only at follow-up phase, the casual and 24-hour BPs at baseline were significantly higher among the subjects in whom the antihypertensive medication was started during the follow-up (**III**: Table 1). No statistically

significant differences were found in BP, LVM or LVMI values in subjects with and without antihypertensive medication at follow-up phase (**III**: Table 2).

3.1 Predictive value of ambulatory vs. casual blood pressure

The analyses included the subjects without antihypertensive medication on whom echocardiography data was available at follow-up (n=66). The predictive value of ambulatory BP was compared with that of casual BP in the prediction of future LVMI. Both the BP levels and LVMIs were analysed as continuous variables (**III**).

The follow-up LVMI was best predicted by 24-hour PP (r=0.308, p=0.012), night-time PP (r=0.291, p=0.018), daytime PP (r=0.253, p=0.041) and casual SBP (r=0.212, p=0.088). The best model in predicting future LVMI included 24-hour PP, subject´s positive family history of hypertension, BMI and age (adj.R^2=0.197) (**III**: Table 3). Both the daytime (adj.R^2=0.180) and the night-time (adj.R^2=0.175) BP models also slightly improved the predictive value of the casual BP model (adj.R^2=0.140) on future LVMI. PP was the BP variable included in all the final models concerning ambulatory BP monitoring, while SBP entered into the final casual BP model. DBP did not have a predictive value. Family history of hypertension, age and BMI of the subjects´ personal characteristics improved also the prediction of future LVMI. None of the cardiac parameters (LVEDD, LVESD, LVPWT, IVST, RWT or FS) could be predicted as well as LVMI.

3.2 Predictive value of blood pressure responses vs. casual blood pressure

The analyses included the subjects without antihypertensive medication on whom echocardiography data was available at follow-up (n=66). The predictive value of BP responses to postural and exercise tests was compared with that of casual BP in the prediction of future LVMI. Both the BP levels and LVMIs were analysed as continuous variables. The analyses were performed separately for BP levels achieved in the tests and BP changes from the reference level during the tests (**IV**).

The best BP variables achieved in the tests in predicting future LVMI were PP at supine test (r=0.337, p=0.006), PP at dynamic exercise last work load (r=0.332, p=0.006) and PP after dynamic exercise (r=0.316, p=0.010). For casual BP, SBP correlated best, but not significantly with future LVMI (r=0.212, p=0.088). Casual DBP or DBP in the tests did not correlate significantly with future LVMI. The best model among BPs achieved in the tests in predicting LVMI included PP after dynamic exercise, family history of hypertension and BMI (adj.R^2=0.207) (**IV**: Table 3). The supine test model, including supine PP, BMI and family history of hypertension, predicted LVMI similarly (adj.R^2=0.195). The predictive value of the casual BP model, including casual SBP, BMI, family history of hypertension and age, was slightly weaker (adj.R^2=0.140). The predictive value of the BP changes from the reference level was also analysed, but it was not as good as the BPs achieved during the tests.

3.3 Prediction of change of left ventricular mass

Echocardiography data was available both at baseline and at follow-up from 70 of the subjects, of whom 52 did not use antihypertensive medication at the

follow-up phase. When analysing the 70 subjects, the LVMI values at baseline were significantly higher among the subjects in whom the antihypertensive medication was initiated during the follow-up (117.9 g/m²; SD 22.43) than among the subjects who were without medication at follow-up phase (106.1 g/m²; SD 19.22) (p=0.04).

In the subjects without antihypertensive medication LVMI changed on average by +23.2 g/m² (95% CI +17.26 to +29.18), whereas in the subjects with antihypertensive medication the change was +7.5 g/m² (95% CI –5.95 to +21.03) (p=0.015). Baseline LVMI correlated significantly with future LVMI among the subjects who did not use antihypertensive medication at follow-up (r=0.508, p<0.0001), while in the medicated subjects the correlation between the baseline and follow-up LVMI was not significant (r=0.392, p=0.108).

When analysing the unmedicated subjects (n=52), the baseline LVMI predicted future LVMI well (adj.R^2=0.243) (**IV**: Table 4). Casual BP did not improve the predictive value of baseline LVMI on future LVMI. Concerning ambulatory BP monitoring, the best model in predicting future LVMI included baseline LVMI, 24-hour PP and age (adj.R^2=0.341). The best model among the BPs achieved in the tests included baseline LVMI, PP at supine test and age (adj.^{2}=0.350). All the models of BPs achieved in test improved the predictive value of baseline LVMI on future LVMI, and in those models PP was the BP variable which was always included in the final prediction model.

Table 4. Prediction of future casual and ambulatory 24-hour BP

The final prediction models have been described in detail in the original publications. These tables show the predictive value of casual BP, ambulatory BP and BP responses. Only those models, which improved the predictive value of casual BP on future BP are presented here. The original tables show all the models and also the different BP components in the final prediction models.

Table 4a. Prediction of casual BP after 10 years

Prediction of casual SBP

BP variables	adj.R^2
Casual BP	0.36
Ambulatory BP monitoring	
24-hour mean BP	0.42
BP responses to tests:	
pre-exercise	0.38
standing	0.39
isometric exercise	0.39
supine	0.44
recovery after dynamic exercise	0.45

Prediction of casual DBP

BP variables	adj.R^2
Casual BP	0.26
Ambulatory BP monitoring	
24-hour mean BP	0.30
BP responses to test:	
recovery after dynamic exercise	0.28

Table 4b. Prediction of ambulatory 24-hour BP after 10 years

Prediction of 24-hour SBP

BP variables	adj.R^2
Casual BP	0.28
Ambulatory BP monitoring:	
daytime mean BP	0.37
night-time mean BP	0.39
24-hour mean BP	0.54
BP responses to tests:	
last work load at dynamic exercise	0.30
isometric exercise	0.35
pre-exercise	0.36
standing	0.37
recovery after dynamic exercise	0.39
supine	0.45

Prediction of 24-hour DBP

BP variables	adj.R^2
Casual BP	0.21
Ambulatory BP monitoring:	
24-hour mean BP	0.29
BP responses to tests:	
last work load at dynamic exercise	0.25
standing	0.25

Table 5. Prediction of future need for antihypertensive medication

The final prediction models have been described in detail in the original publications. This table show the predictive value of casual BP, ambulatory BP and BP responses. Only those models, which improved the predictive value of casual BP on future need for antihypertensive medication are presented here. The original tables show all the models and also the different BP components in the final prediction models.

Table 5. Prediction of need for antihypertensive medication after 10 years

Predicting variables	**Cox-Snell R^2**
Casual BP	0.16
Ambulatory BP monitoring:	
night-time BP (mean and RV80)	0.19
24-hour BP (mean and RV80)	0.26
daytime BP (mean and RV80)	0.27
daytime, night-time and 24-hour BP (mean and RV80)	0.40
BP responses to tests:	
standing	0.20
last work load at dynamic exercise	0.20
isometric exercise	0.21
supine	0.23
pre-exercise	0.26

Table 6. Prediction of future LVMI

The final prediction models have been described in detail in the original publications. These tables show the predictive value of casual BP, ambulatory BP and BP responses. Only those models, which improved the predictive value of casual BP on future LVMI are presented here. The original tables show all the models and also the different BP components in the final prediction models.

Table 6a. Prediction of LVMI after 10 years (echo-data at follow-up)

Predicting variables	**adj.R^2**
Casual BP, personal characteristics	0.14
Ambulatory BP monitoring, personal characteristics	
daytime BP, personal characteristics	0.18
night-time BP, personal characteristics	0.18
24-hour BP, personal characteristics	0.20
BP responses to tests, personal characteristics:	
standing, personal characteristics	0.15
pre-exercise, personal characteristics	0.17
last work load at dynamic exercise, personal characteristics	0.17
supine, personal characteristics	0.20
recovery after dynamic exercise, personal characteristics	0.21

Table 6b. Prediction of LVMI after 10 years (echo-data also at baseline)

Predicting variables	**adj.R^2**
Baseline LVMI	0.24
Ambulatory BP monitoring, personal characteristics	
night-time BP, personal characteristics	0.33
24-hour BP, personal characteristics	0.34
BP responses to tests, personal characteristics:	
work load 2, personal characteristics	0.28
isometric exercise, personal characteristics	0.29
last work load at dynamic exercise, personal characteristics	0.30
pre-exercise, personal characteristics	0.32
recovery after dynamic exercise, personal characteristics	0.32
standing, personal characteristics	0.34
supine, personal characteristics	0.35

DISCUSSION

1. Subjects

There were some major, partially unique strengths in the present 10 years of follow-up. The subjects were a well-defined group of healthy normotensive, newly diagnosed borderline or mildly hypertensive middle-aged men who were not taking any medication at baseline. In addition, they were volunteers from a population-based survey. At baseline, a comparable number of participants with different BP status was tried to be included in the study, which explains the relatively high number of the subjects with elevated BP at baseline. The return rate, 90%, was excellent after such a long follow-up. It is difficult to evaluate the exact significance of the loss of 10 subjects from the original cohort of 97 subjects. However, the 10 subjects who failed to attend the follow-up were distributed equally between the original BP groups: three normotensive, three borderline hypertensive and four mildly hypertensive subjects. The population registry confirmed that none of them had died. Two of them refused to participate in the follow-up study for personal reasons, and eight subjects did not answer the letter of invitation. Most of them had moved to another town, and one had moved abroad.

Concerning study limitations, the study sample was relatively small as a consequence of the intra-arterial BP monitoring method used at baseline. However, the present follow-up is, to my knowledge, the largest prospective study using intra-arterial 24-hour ambulatory measurements in an outpatient setting in predicting future BP, need for antihypertensive medication and LVM of originally normotensive, borderline and mildly hypertensive untreated men.

The subjects were not selected with regard to any important characteristics, except male gender, age 35 to 45 years and white race. Thus, the findings may not apply to women, different age distribution and non-white populations. In addition, the basis for antihypertensive therapy for the participants had not been standardized. The decision of initiation of antihypertensive medication was left to the primary care physicians, assuming that they were following the existing guidelines. On the other hand, the circumstances were optimized as far as possible by giving a written summary of the results for the primary care physician to take them into consideration in the clinical decision making. Under the present circumstances within the public health care the subjects who were started antihypertensive medication were very likely hypertensive before the medication but, on the other hand, some of the hypertensive subjects did not have antihypertensive medication at follow-up. The analysis of the prediction of future need for antihypertensive medication has limitations, but also that analysis was worthwhile since it strengthened the determination of subjects´ future BP status.

2. Methods

The original BP classification system (WHO Expert Committee 1978) was used in the present follow-up, although the most recent classification systems might better reflect the hypertension-related CV risk by defining the lower limits of hypertension as 140 mmHg of SBP and 90 mmHg of DBP (The sixth report of the Joint National Committee 1997, WHO Guidelines Subcommittee 1999). However, those most recent guidelines have also stated that the relationship between the level of BP and the risk of CV events is continuous, and that the arbitrary nature of the definition of hypertension has contributed to the variation

in the definitions issued by various national and international authorities. In the present study, the classification system did not affect the results, because the analyses concerning prediction of future BP level, need for antihypertensive medication and LVM were performed by using subjects´ BPs as continuous variables.

By using two BP measuring methods at both follow-up phases, it was possible to compare their predictive value and also to clarify whether the use of a more accurate one could improve the prediction of future BP level, need for antihypertensive medication and LVM. In addition, casual BP was evaluated by means of multiple carefully standardized measurements made on two or three visits. It has been suggested that the closeness of the association between casual BP and hypertension-related target-organ damage increases if casual BP is measured with multiple measurements and several visits to a clinic (Verdecchia et al. 1999). Intra-arterial ambulatory BP was used at baseline, because it was the best method available for BP measurement, and it was accepted for research work. At follow-up, ambulatory BP was measured non-invasively, because the invasive measuring method was no longer acceptable for ethical reasons.

Concerning the ambulatory BP monitoring, day- and night-time were defined by the clock-time dependent method and, on the other hand, by the narrow method which exclude data from the morning and evening transition periods (Fagard et al. 1997a). Supine body position at night, and a position of the cuffed arm relative to the heart, which have recently been found to influence the measurements at night were not taken into account (Parati 2000). However, by using the intra-arterial BP recording method only minimal disturbance to the subjects´ sleep was caused. The classification of “dippers” and “non-dippers”, which has been shown to be poorly reproducible, was not used at 10 years of follow-up (Mancia et al. 1997).

The protocol of the study allowed the comparison of the predictive value of BP responses to different postural and exercise tests in the same study. The predictive value of both the achieved BP levels during the tests, and BP changes from the reference level could also be compared. Most of the previous studies have used either BP levels in the tests or BP changes from the reference level as predictors (Dlin et al. 1983, Fixler et al. 1985, Radice et al. 1985, Sparrow et al. 1986, Chaney et al. 1988, Tanji et al. 1989, Wilson et al. 1990, Guerrera et al. 1991, Matthews et al. 1993, Manolio et al. 1994, Everson et al. 1996, Allison et al. 1999, Singh et al. 1999, Miyai et al. 2000). During the tests, intra-arterial monitoring allowed exact measurement of both SBP and DBP level. DBP findings have been rarely reported during exercise tests because of the concern about the accuracy of DBP measurements by non-invasive methods (Pickering 1987). In the dynamic exercise test the final level of the exercise was standardized by defining the age-specific maximum HR by the formula: 205 – subject´s age (years)/2. By using the submaximal exercise test the possible influence of exercise to BP level of the subsequent hours and the following day was minimized. The BP levels were analysed as continuous variables, avoiding the arbitrary nature of any classification (The sixth report of the Joint National Committee 1997, WHO Guidelines Subcommittee 1999).

All the echocardiography studies both at baseline and at follow-up were performed by the same cardiologist who was unaware of the subjects´ BP and clinical status. At baseline the interobserver agreement was also examined and found to be good. In addition, the studies were performed both at baseline and at follow-up by using only one echocardiography device accepted for clinical work.

The number of potential predictor variables was relatively large in this study. On the other hand, a large amount of explaining variables and models

strengthens the reliability of the results by showing that the explaining factors were taken carefully into consideration. Separate clusters were used to avoid large amounts of explaining variables in an individual prediction model. In addition, in particular the stepwise variable selection methods were applied within clusters in order to achieve the best prediction model. By using the adjusted coefficients of determination the models including different numbers of explaining variables could be compared reliably. Thus, the multivariate analyses were planned especially carefully by taking into consideration the characteristics and size of the study sample.

4. Results

4.1 Prediction of future blood pressure level

In the present 10 years of follow-up the changes in BP classification groups had further advanced as compared to the 5-year follow-up of the same study population (Majahalme et al. 1996). These findings are in concordance with studies where an increase in BP levels has been noticed with age (Kannel 1996). The borderline hypertensive group was most unstable, which also confirmed the earlier findings of some studies (Leitschuh et al. 1991, Faire et al. 1993). The subject´s personal characteristics were included at the 10-year follow-up for the first time in the BP level analyses, but they did not improve the predictive value of baseline BP variables on future casual or ambulatory BP.

In the present study, the predictive value of intra-arterial 24-hour SBP was 6.5% better than that of baseline casual SBP when predicting future casual SBP, and the predictive value of intra-arterial 24-hour DBP was 4% better than that of

baseline casual SBP and DBP when predicting future casual DBP. When comparing with the 5-year follow-up (Majahalme et al. 1996), the predictive effect of both 24-hour SBP and DBP was slightly improved when comparing with the predictive value of baseline casual BPs. However, especially the predictive value of intra-arterial 24-hour SBP compared to casual SBP in predicting 24-hour SBP increased from 7% to 26.5%. In the prediction of 24-hour DBP, the predictive effect of intra-arterial 24-hour DBP compared to casual DBP increased from 3% to 8%. Since the hypertension-related target-organ damage has been shown to correlate more with SBP than with DBP (Kannel et al. 1969b, Kannel et al. 1970, Stokes III et al. 1989, Neaton and Wentworth 1992, Lindenstrom et al. 1995, Klag et al. 1996, He et al. 1999), especially the exact prediction of SBP is of great importance. The present findings showed that by monitoring 24-hour BP, the prediction of future BP, especially 24-hour SBP can be improved. On the other hand, the present findings confirmed that the 24-hour monitoring cannot be replaced by shorter monitoring periods including only daytime or night-time BPs without loosing some predictive value, although some have suggested that the average of a few shorter monitoring periods could also be useful (Weber et al. 1982, Clement et al. 1984).

The BP responses to the postural and exercise tests also improved the predictive value of casual BP on future BP level. Interestingly, the predictive value of the simple postural tests and the best exercise tests was approximately the same. The predictive value of postural tests has been found also in previous studies (Drummond 1985, Sparrow et al. 1986, Parker et al. 1987). Concerning the dynamic exercise test, especially the BP levels at 10 minutes after exercise were predictive, which has been suggested also by some other studies (Singh et al. 1999). Unlike most of the previous studies, the present follow-up allowed the comparison of BP responses measured as BPs achieved in tests and BP changes

from the reference level in the same study. The results confirmed that the BP responses were more predictive when the BP levels achieved during the tests were determined. By including the SBPs and DBPs in the same prediction model, their predictive value could also be compared. The analyses showed that the predictive value of baseline casual DBP on future casual DBP was so weak that also casual SBP was included in the final prediction model. The other models concerning the prediction of future SBP or DBP level included only SBP or DBP as a final predictor variable. The predictive effect of the BP responses was so strong that the subjects´ personal characteristic variables did not enter into any final prediction model of future BP.

4.2 Prediction of future need for antihypertensive medication

The prediction of future need for antihypertensive medication was analysed for the first time at 10 years of follow-up. When predicting the need for antihypertensive medication, the best combinations of explaining variables were sought. To my knowledge, the present study demonstrated, for the first time, that BP variability (RV80) is able to improve the predictive value of mean BP on future need for antihypertensive medication. Previously, Parati et al. (1987) have concluded that high BP may adversely affect target-organs not only through its 24-hour mean value but also through the extent of BP variability.

In addition, this study provided the first evidence that by using the anticipatory BP response to the dynamic exercise test, by measuring the BP level before the test initiation, the predictive value of casual BP on future need for antihypertensive medication can be improved. Everson et al. (1996) have earlier shown an association between anticipatory BP response to dynamic exercise test and incidence of hypertension or high BP in an unselected population. The

subjects´ personal characteristics did not improve the predictive value of BP responses on future need for antihypertensive medication.

4.3 Prediction of future left ventricular mass and it´s change

This study, like some of the previous ones, confirmed the value of ambulatory BP over casual BP measurements in predicting echocardiographically determined LVH (Verdecchia et al. 1990, Muiesan et al. 1996a, Fagard et al. 1997b, Mancia et al. 1997, Khattar et al. 1999, Mancia and Parati 2000). However, most of these earlier studies have been cross-sectional and, before the present study, only the study published by Khattar et al. (1999) has reported a follow-up time of several years. The diurnal variation of BP did not improve the prediction of future LVM in the present follow-up. The meta-analysis of 19 comparative studies has also indicated that the predictive value of the daytime and the night-time BPs is approximately the same, indicating that these BP values have a close relationship with each other (Fagard et al. 1995a). When analysing the predictive value of different BP components, ambulatory PP proved to be a significant, and the best predictor of future LVM. The predictive value of PP on LVM has been confirmed in very few previous studies, and none of them has been prospective in nature before the present follow-up (Pannier et al. 1989, Khattar et al. 1997, Baguet et al. 2000). The most predictive variables of the subjects´ personal characteristics were BMI and positive family history of hypertension. Both weight and BMI have been shown also in the previous studies to independently associate with LVM (Levy et al. 1988, Khattar et al. 1997). There is evidence also that heredity has a small, but independent effect on increased LVM (Post et al. 1997, Schunkert et al. 1999). Antihypertensive medication affected significantly to the development of cardiac mass. This finding is in good concordance with previous reports showing, that antihypertensive medication reduces LVM as a consequence of BP reduction,

but also through BP independent effects of different drugs, which are disparate of the magnitude of BP reduction (Gottdiener et al. 1997, Schmieder et al. 1998, Verdecchia et al. 1998a).

The present study also showed that BP responses to the postural and exercise tests improved the predictive value of casual BP on future LVM. Most of the earlier findings concerning the relationship between BPs in tests, and echocardiographically determined LVH have been cross-sectional (Ren et al. 1985, Gottdiener et al. 1990, Michelsen et al. 1990, Schmieder et al. 1990, Lauer et al. 1992, Schimizu et al. 1992, Trieber et al. 1993, Vriz et al. 1995, Georgiades et al. 1996, Allen et al. 1997, Molina et al. 1999, Kamarck et al. 2000), and the prospective evidence is very limited (Markovitz et al. 1996, Georgiades et al. 1997, Kapuku et al. 1999). This study is the longest population-based follow-up showing evidence of the predictive value of BP responses to the tests over casual BP measurements. Likewise, in the study of ambulatory BP monitoring, also in the analyses of BP responses the predictive value of PP was the best. Nobody has earlier shown a predictive value of test PPs on future LVM. The best predictors were again the postural and dynamic exercise tests. Concerning the dynamic exercise test, especially the BPs at pre-exercise, at last work load and at recovery were predictive.

The mean changes observed in LVM were +20.4g among subjects with antihypertensive medication at follow-up and +46.7g among subjects without antihypertensive medication. At baseline, when inter-observer agreement was assessed, the difference, when analysing subjects´ LVMs, was only 5.8g (coefficient of repeatability = 22.8) between the two cardiologists. Thus, the changes observed in cardiac mass were out of the inter-observer agreement. Baseline LVM predicted future LVM significantly only among unmedicated subjects, showing the importance of antihypertensive medication on the

development of future LVM. Although the predictive effect of baseline LVM was taken into account, the ambulatory BPs and BP responses to the tests were able to improve the prediction of future LVM.

SUMMARY AND CONCLUSIONS

The present investigations were designed to examine the role of casual BP measurements, ambulatory 24-hour BP levels and variability in the prediction of future BP level, need for antihypertensive medication and LVM. The aim of these studies was also to determine the importance of different components of BP, and the BP responses to different postural and exercise tests as predictors. In addition, the predictive value of subjects´ personal characteristics and baseline LVM measurements on future LVM was evaluated.

The major findings and conclusions are:

1. The predictive value of the ambulatory BP, especially 24-hour mean BP, is better than that of casual BP on future casual and ambulatory BP level, need for antihypertensive medication and LVM. Also casual BP is able to predict future BP level, need for antihypertensive medication and LVM, but its predictive value does not reach that of ambulatory BP although the casual measurements were performed most carefully by using multiple standardized measurements.

2. The 24-hour ambulatory monitoring cannot be replaced by shorter 5-hour monitoring periods including only daytime or night-time BP values without loosing some of the predictive value.

3. By using intra-arterial ambulatory BP variability, determined as RV80 variables in addition to mean BP values, the prediction of future need for antihypertensive medication can be improved.

4. The future SBP level is more predictable than the DBP level and, on the other hand, the baseline SBP is a better predictor of future BP level than DBP.

5. The BP responses to the postural and exercise tests improve the predictive value of casual BP measurements on future BP level, need for antihypertensive medication and LVM.

6. Concerning the dynamic exercise test, especially the BP levels at pre-exercise and at 10 minutes after exercise are promising. However, the predictive value of the simple postural tests and the dynamic exercise test is approximately the same. Thus, concerning the predictive value of simple postural tests, they could be more suitable for routine clinical practice. However, when a lot of exercise tests are performed in clinics, high BP levels achieved during tests should be identified and it should be considered whether a closer follow-up of BP is warranted.

7. The BP levels achieved during the tests are more predictive than the BP changes from the reference level.

8. Only part of the variance of LVM can be explained by BP and other variables used in the present study as predictors.

9. The PP, as a pulsatile component of BP, is strongly related to the development of future LVM. Thus, the LV ejection and the properties of

the arterial wall, which are the main determinants of subjects´ PP level, are probably of great importance to the development of future LVM.

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