Exercise and cardiovascular risk reduction

Citation for published version (APA):

Wijnen, J. A. G. (1994). *Exercise and cardiovascular risk reduction*. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht. <https://doi.org/10.26481/dis.19941221jw>

Document status and date:

Published: 01/01/1994

DOI:

[10.26481/dis.19941221jw](https://doi.org/10.26481/dis.19941221jw)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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EXERCISE AND CARDIOVASCULAR
RISK REDUCTION

CIP-DATA KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Wijnen, Joseph Anna Guillaume

Exercise and cardiovascular risk reduction / Joseph Anna
Guillaume Wijnen. - Maastricht : Universitaire Pers
Maastricht. - Ill.

Thesis Maastricht. - With ref. - With summary in Dutch.
ISBN 90-5278-165-6

Subject headings: exercise and cardiovascular diseases /
exercise and hypertension / antihypertensives

This thesis was supported, in part, by Funds from the Dutch Ministry of Welfare, Health and
Cultural Affairs and SmithKline Beecham BV

Publicatie van dit proefschrift werd mogelijk gemaakt dankzij een opleidingsgrant van
AOV/ABP

EXERCISE AND CARDIOVASCULAR RISK REDUCTION

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Rijksuniversiteit Limburg te Maastricht,
op gezag van de Rector Magnificus, Prof. dr. H. Philipsen,
volgens het besluit van het college van Dekanen,
in het openbaar te verdedigen
op woensdag 21 december 1994 om 14.00 uur

door

Joseph Anna Guillaume Wijnen

geboren te Maastricht in 1958

UNIVERSITAIRE PERS MAASTRICHT

Promotor

Prof. dr. H.A.J. Struijker Boudier

Co-promotores

Dr. M.A. van Baak

Dr. L.M.A.B. Van Bortel

Beoordelingscommissie

Prof. dr. H. Kuipers (voorzitter)

Prof. dr. R.H. Fagard, Katholieke Universiteit Leuven

Prof. dr. J.W. van Ree

Prof. dr. W.H.M. Saris

Dr. J.L.R.M. Smeets

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cause CHD. Nevertheless, there is an increasing body of evidence supporting the independence of a direct relationship of LDL-cholesterol and the inverse relationship of HDL-cholesterol to the risk of developing CHD (6, 7).

2.2 Is physical inactivity a risk factor for cardiovascular disease?

Several lines of evidence from epidemiological studies, clinical trials, and intervention studies indicate physical inactivity is an important risk factor to develop cardiovascular disease in different ways.

2.2.1 Direct effect

Pesenti et al (8), reviewing the literature on the topic of habitual physical activity in the primary prevention of CHD, concluded that the relative risk for CHD of physical inactivity appears to be similar in magnitude to that of hypertension, hypercholesterolemia and smoking. In a more positive way, it might be anticipated that regular exercise protects against cardiovascular

voor Karin
aan mijn ouders

from 1945 to
1950 and 1955 to 1960

CHAPTER 1

General introduction

1. GENERAL INTRODUCTION

Large epidemiologic investigations (1, 2, 3) have established three major and independent factors that predict the mortality risk of cardiovascular disease, especially of coronary heart disease (CHD). Blood pressure (BP), serum total cholesterol and cigarette smoking have a continuous positive association with major cardiovascular events (4) and a distinct escalation of risk is noted for combinations of these risk factors (2). Other factors have been frequently associated with the pathogenesis of CHD, such as obesity (body mass index), high alcohol consumption, hyperglycemia, hyperinsulinemia, elevated serum levels of uric acid, triglycerides, low-density lipoproteins (LDL) and low serum levels of high-density (HDL) lipoproteins, although their independent predictive ability after allowance for the standard risk factors is doubted by some (5). Nevertheless, there is an increasing body of data to support the independence of a direct relationship of LDL-cholesterol and the inverse relationship of HDL-cholesterol to the risk of developing CHD (6, 7).

1.1 *Is physical inactivity a risk factor for cardiovascular disease?*

Several lines of evidence from epidemiological studies, cross-sectional observations and intervention studies implicate physical inactivity as an important risk factor to develop cardiovascular disease, in different ways.

1.1.1 *Direct effect*

Powell et al (8), reviewing the literature on the role of habitual physical activity in the primary prevention of CHD, concluded that the relative risk for CHD of physical inactivity appears to be similar in magnitude to that of hypertension, hypercholesterolemia and smoking. In a more positive way, it might be anticipated that regular exercise protects against cardiovascular

disease. However, one should bear in mind that evidence for this relationship is derived from observational and prospective epidemiological studies. To establish a true cause effect relationship, a large clinical trial is required in which healthy individuals are randomly assigned to different activity patterns ranging from low to high activity levels of different durations, and with and without sufficient intensity to improve cardiovascular fitness (a training status). Those trials have not been performed yet and their feasibility can be questioned, because of high costs, logistic and ethical problems and they would be accompanied by a high attrition rate associated with exercise.

Studies relating physical activity on the job with the incidence of CHD found that workers in physically demanding jobs have a decreased risk of CHD in comparison to their sedentary counterparts (9-13). Paffenbarger and colleagues (14, 15) followed longshoremen for 22 years and showed that after adjustments for all major risk factors and post-morbid job transfers men in the highest work activity category had a fatal heart attack rate of only half that of men in the lowest work activity category. In the Framingham study (16), overall mortality and mortality due to cardiovascular and ischemic heart disease were inversely related to the level of physical activity for men but not for women. In a later study of the Framingham cohort (17), improved overall, cardiovascular and coronary mortality was found with increasing levels of 24-hour physical activity in men over a period of 24 years. These mortality benefits applied to both individuals with as well as individuals without intervening overt cardiovascular disease, and was not significantly related to physical demand on the job.

More recent studies have addressed the role of leisure time activity in the prevention of cardiovascular disease. Harvard alumni were followed after graduation (18) and a strong inverse relation was found between habitual exercise and total cardiovascular disease. Sedentary alumni, exercising less than 500 kcal/week, were at 49% greater adjusted risk for a heart attack compared to the most active men (≥ 2000 kcal/week). Other studies (19, 20) suggest that especially vigorous aerobic exercise that has to be habitual, and not high totals of physical activity per se, is protective against non-fatal and fatal CHD. Supportive for this suggestion is a study (21) that showed that habitual high intensity leisure time activity ($> 60\% \text{VO}_{2\text{max}}$) reduced the risk of primary cardiac arrest by 40% compared to low and moderate intensity activity. Furthermore, it has been shown that although the risk of cardiac arrest is transiently increased during vigorous exercise, it is much more increased in sedentary individuals (22).

Physical fitness and regular physical activity are related (23, 24) although they cannot be regarded as synonymous (23, 25). Fitness level depends on genetic endowment, characteristics of the individual and kind, frequency and duration of the activities performed. Initial physical fitness, measured either by maximal treadmill test or maximal cycle ergometry has been found to be predictive for future development of manifestations of cardiovascular disease

Table 1. Possible direct mechanisms for preventing CHD and CVD by regular physical activity based on ref 8,24,29

-
- Decreased myocardial work and oxygen demand
 - Enhanced myocardial function
 - Improved myocardial oxygen delivery or utilization
 - Enhanced myocardial electrical stability
 - Modification in structure of the coronary arteries
 - Retardation or regression of atherosclerosis
 - Reduction of (coronary) vasospasm
 - Increased fibrinolytic activity
 - Reduction in aggregability of platelets
-

(26-28). A lower level of physical fitness is associated with a higher risk of death from CHD and cardiovascular disease in healthy men, independent of conventional coronary risk factors, HDL and LDL-cholesterol (24).

A strong and graded association between physical fitness and mortality due to all causes, cardiovascular disease and cancer for both men and women has been found (24, 28).

Table 1 summarizes direct mechanisms by which regular physical activity could prevent CHD and cardiovascular disease (CVD), as suggested by the literature (8, 24, 29).

1.1.2 Indirect effect(s)

Cross-sectional studies found a direct inverse relationship between levels of fitness, levels of physical activity and risk factors for cardiovascular disease. In men (30), a consistent, inverse relationship between physical fitness categories and resting heart rate, body mass, percentage body fat, serum levels of cholesterol and triglycerides, glucose and systolic blood pressure (SBP) was observed. In women (31), physical fitness was independently associated with low serum triglycerides, high HDL-cholesterol, low total cholesterol/HDL-ratio, and low blood pressure. Several studies in young, middle-aged and older men reported cross-sectional associations between levels of physical activity and CHD risk factors (32-36). For example, in older Dutch men generally favorable associations were found between total weekly physical activity and specific activities, such as gardening and walking, and serum cholesterol and SBP (36). Even in a physically active, middle-aged population, subjects who were physically more fit and physically more active had better cardiovascular risk profiles based on body fat, blood pressure and smoking habits, than subjects who were less active and less fit (37).

Physical activity is associated with decreases in adiposity among younger and middle-aged populations, independent of caloric intake (38). Regular

physical activity may prevent the development of non-insulin-dependent diabetes mellitus (39, 40).

Further support for the hypothesis that physical activity can favorably alter risk factors can be obtained from numerous training studies. Most studies have demonstrated that chronic exercise is associated with lower resting BP (41). Individuals who participated in training studies have shown increased HDL cholesterol levels (42-45), decreased LDL-cholesterol levels (42) and increases in HDL-cholesterol/total cholesterol ratio (43). Physical exercise has been shown to improve glucose tolerance and insulin sensitivity (46, 47).

Is physical inactivity a risk factor for hypertension?

Blood pressure is consistently and quantitatively related to the risk of developing all three major manifestations of cardiovascular disease: coronary heart disease, stroke and transient ischemic attacks, and congestive heart failure (48). In the general population, risks are lowest for adults with an average SBP less than 120 mmHg and an average DBP less than 80 mmHg. The higher the SBP, the higher the risk of premature cardiovascular death. The same holds for DBP although SBP is a better predictor (48). Although by convention the term hypertension is used to denote SBP and DBP in adults that exceed 140 and 90 mmHg, high normal BP (SBP 130-139 mmHg, DBP 85-89 mmHg) requires frequent monitoring and lifestyle measures because of the increased risk of developing definite hypertension and non-fatal and fatal cardiovascular events (49).

There are certain risk factors that increase the probability of developing hypertension. About one fourth of normotensive subjects and approximately one half of the hypertensive population can be characterized as sodium-sensitive, meaning that excess sodium in their diets increases their blood pressures (50). Obese persons have a higher likelihood of becoming hypertensive than the non-obese do (51). Excess alcohol ingestion increases blood pressure (52). There is a growing body of evidence that associates a sedentary lifestyle with high blood pressure.

Paffenbarger et al (53) followed nearly 15,000 Harvard male alumni for 6-10 years. Alumni who did not engage in vigorous sports play were at 35% greater risk of hypertension than those who did, at all ages. Blair and colleagues (54) found that risk of developing hypertension was substantially increased with increasing baseline BP after a follow-up of 1-12 years. After adjusting for sex, age, baseline BP, and body mass index, persons with low levels of physical fitness had a relative risk of 1.52 for the development of hypertension when compared to highly fit persons.

Fifteen endurance exercising adult males and 15 matched non-exercising males were followed for 20 years in a study by Kasch et al (55). Resting BP was found to be considerably higher on follow-up in the non-exercising group. Whereas two men in the exercise group and three in the control group were

initially hypertensive, after 20 years six of the non-exercisers became hypertensive and none in the exercise group.

A graded, inverse association was shown between total weekly physical activity and mean BP in a large random sample of a Finnish male population (56). Total weekly physical activity and specific activities as gardening and walking were favorably associated with SBP in a representative sample of older Dutch men (36). In the Minnesota Heart Survey (34), greater heavy intensity activity during leisure time was reported to be associated with lower SBP in women, but not in men.

Several studies have shown that the level of physical fitness is independently and inversely related to SBP after adjustments for possible confounders such as age, body mass and body fat (30-32, 57). This relationship was found in middle-aged and older populations, for both men and women (30, 31) and in children (32, 57). Even in a fit and active middle-aged population this association was found (37). In general, DBP is not related to physical fitness (30, 31, 57).

Most of the exercise intervention studies show a reduction in resting BP in both normotensive and hypertensive subjects. This will be discussed in more detail, in the next section.

In summary, studies have demonstrated that physical fitness and physical activity, be it occupational or recreational, is associated with decreased risks of coronary heart disease and hypertension.

1.2 The effect of chronic exercise on blood pressure

The achievement of long-term blood pressure control in persons prone to hypertension or with mild hypertension is of central strategic concern in the prevention of cardiovascular morbidity and mortality. Chronic aerobic exercise has been suggested as an effective and physiologically desirable non-pharmacological approach that can be used (a) in the strategy of prevention of hypertension, (b) as a definite intervention, and (c) as an adjunct to pharmacological therapy (58). A reduction in BP with regular participation in aerobic exercise could be due to the accumulative effects of single exercise bouts rather than actual long-term adaptations to exercise training. Post-exercise hypotension ranging from 10-25 mmHg for SBP and 5-10 mmHg for DBP has been observed 1-4 hours after cessation of aerobic exercise (59-61). In a recent study (62), BP was significantly lowered even up to 13 hours in a group of hypertensive men after a single bout of dynamic exercise. Although this is a much noted observation which needs additional research, most attention has been focussed on the effects of endurance exercise training.

1.2.1 The effect of endurance training on blood pressure at rest

A definite conclusion on the effect of dynamic isotonic training on BP at rest has been seriously hampered by the lack of well designed, controlled and

randomized studies (41, 63). Extensive variability in design has further complicated the matter. Designs differ with regard to number of subjects studied (range 4-66 subjects), length of training (range 4-52 wk), mode of training (walking, cycling, jogging, combinations), session duration (20-60 min), frequency of training (2 days/week to daily), and intensity (low to high)(41). Various conditions for BP recording have been used and some studies in hypertensives failed to ascertain that subjects had persistent elevations in BP before enrollment (64). Most studies have been limited to male subjects (41, 65). In recent years, more well controlled studies with fewer design deficiencies have been performed (65).

On average, endurance exercise training has been found to lower BP at rest in normotensives by 3-4 mmHg for both SBP and DBP (66, 67). In a meta-analysis of 25 studies examining the BP lowering effects of endurance exercise training on individuals with essential hypertension, the average reduction in SBP by training, weighted for sample size, was 10.8 mmHg for SBP and 8.2 mmHg for DBP (65). In a more recent meta-analysis by Fagard (67) only studies with a control group or period were included. The weighted average training-induced change in BP was -6.2/-6.8 mmHg in borderline hypertensives, and -9.9/-7.6 mmHg in hypertensives. Furthermore, it was noted that controlled studies which followed most rigorous scientific criteria showed the smallest decrease in BP (Table 2).

The intensity of exercise, the weekly frequency, the time per session and the length of the training program did not contribute significantly to the inter-

Table 2. Training-induced changes in BP in controlled studies according to study design

Study design		Change in BP at rest	
		SBP	DBP
Random allocation to control or exercise group <i>with</i> regular contact of subjects during control period	N	-2 (-6 to +3)	-2 (-5 to +0.6)
	H	-7 (-13 to -2)	-5 (-9 to -1)
Random allocation to control or exercise group <i>without</i> regular contact of subjects during control period	N	-4 (-10 to +2)	-3 (-5 to -0.6)
	H	-9 (-18 to 0)	-10 (-11 to -9)
No random allocation to control or exercise group	N	-4 (-7 to -0.5)	-5 (-8 to -1)
	H	-10 (-15 to -5)	-9 (-14 to -3)

Adapted from Fagard (67). Changes in BP (mmHg) and 95% confidence limits. Changes after adjustment for control observations and weighted for number of participants. N, normotensive groups; H, hypertensive groups.

study variance of the BP response in normotensives or hypertensives (67). Some studies (68-70) seem to indicate that low-intensity (50-55% $\text{VO}_{2\text{max}}$) endurance training has the same BP lowering effect as training at a moderate intensity level (70-75% $\text{VO}_{2\text{max}}$). It is not clear how long it takes for endurance training to elicit lower blood pressures, but most studies suggest that BP lowering will likely occur after 3 weeks and before 12 weeks of training have been completed (41). Jennings and colleagues found that exercising for 4 weeks, three times a week for 40 min at 60-70% W_{max} , lowered resting BP by 10/7 mmHg in sedentary subjects (71) and 11/9 mmHg in hypertensive subjects (72). In a later study (73), applying the same protocol in healthy sedentary subjects, they even stated that BP fell 10/6 mmHg after the third training bout at the beginning of the second training week and no further reduction occurred beyond the fourth bout of exercise. Urata et al (74) found resting BP to be reduced after 3 weeks of low-intensity training in mildly hypertensive patients and no further reduction in BP was seen after 7 weeks of training.

Less fit and less active subjects may probably show the largest increase in exercise capacity and the largest reduction in BP following training. This is partially suggested by the meta-analysis of training studies by Fagard (67) who found the response of DBP to be significantly related to the increase in exercise capacity. In addition, in a study amongst Antarctic expeditioners (75), 3 weeks of moderate exercise training significantly lowered BP in the winter, when physical activity was limited to indoor activities because of climatic conditions. In the summer, however, climatic conditions are improved and subjects were more active during work and leisure time. BP at rest in the summer was similar to the post-training levels during the winter and additional moderate training for 3 weeks did not further reduce BP.

At present it is not known whether hypertensive subjects are able to maintain lower blood pressure levels with continuation of training for years. In a study by Jennings et al (76) the supine resting BP of 13 untreated hypertensive patients fell 11/9 mmHg below sedentary levels after one month of moderate endurance exercise three times a week. After one year of exercise three times a week, these lower levels were maintained in all subjects. However, in the second year several patients had a BP returning towards hypertensive levels, despite good compliance to regular exercise.

Finally, many studies have considered weight reduction and change in diet as possible confounding factors. These factors are unlikely to bias the observed hypotensive effect by training (65, 67). Studies that show a statistically significant lowering of BP by training may be more likely to be published than those that do not. To which extent this obscures a definite conclusion on the effect of training on BP, especially in normotensives where the effect is small, is not known.

On cessation of endurance training, BP at rest will return to sedentary levels, usually in several weeks or a few months, depending on training duration (41).

1.2.2 *The effect of endurance training on ambulatory blood pressure*

The majority of training studies suggests that blood pressure at rest is lowered by aerobic exercise in hypertensives and to a lesser extent in normotensives. Most of the evidence is derived from single or repeated indirect measurement of casual BP, or more or less basal BP, in a relatively short span of time. Apart from potential errors and inconsistencies in technique, random variation of BP is large and fluctuations of 40% in BP can occur during the day (77). To detect an anticipated fall by training of 8-10 mmHg (7-10%) in resting BP in a hypertensive population or 3 mmHg (2-3%) in resting BP in a normotensive population (67) could present a difficult problem against this background.

Ambulatory monitoring of BP can play an important role in improving the precision of a trial and minimizing the number of subjects required by reducing within-subject variability of BP, by the greater number of observations (77). Furthermore, levels of BP measured under resting conditions in a laboratory often overestimate levels measured throughout the entire day under free-living conditions (78). Ambulatory pressure measurements are fairly reproducible (79), correlate usually better with left ventricular mass (index) than casual pressure (80), and are free of confounding factors, such as the alerting response (77). In longitudinal studies, casually determined pressures can decrease over time without corresponding changes in levels measured by ambulatory monitoring (81). Moreover, it is of interest to study the effect of training on the circadian pattern of BP during the day, whereby BP reaches its highest level at mid-morning, to fall thereafter throughout the day to its nadir during sleep with a rise again before or at waking (82).

The technique of ambulatory BP measurement has only recently been introduced in training studies (Table 3a and 3b). Together, the results of these investigations indicate that low- to moderate-intensity aerobic exercise training has, if any, only a small effect on 24-hour levels of arterial BP in normotensive or mildly hypertensive subjects. All, but one (88), found no effect of training on night-time BP. Some studies (86, 88) found ambulatory BP lowered by training without a concomitant decrease in BP at rest.

1.2.3 *The effect of endurance training on blood pressure during exercise*

Relatively few controlled training studies have presented interpretable BP data during steady-state submaximal exercise (65, 67). The majority of studies compared exercise BP at the same absolute submaximal workload, whereas four studies (68, 71, 83, 89) compared exercise BP at similar relative workloads before and after training and one study (72) compared exercise SBP at a percentage of predetermined baseline $W_{\max}$ before and after training. A reduction in BP at the same absolute workload following training could be the

Table 3a. Effects of training on resting and ambulatory blood pressure. Longitudinal controlled studies. *Study design*

Investigator	Ref.	Group	n	Age	Sex	Duration of training (weeks)	Mode of training	Frequency (per week)	Session duration (min)	Intensity
Van Hoof (1989)	83	N	26	39 ± 10	M	16	Combin.	3	60	?
Gilders (1989)	84	N	10	41 ± 9 (SE)	M,F	16	bicycle	3	30	70% VO _{2max}
		BH/H	7	46 ± 2 (SE)	M,F	16	bicycle	3	30	70% VO _{2max}
Somers (1991)	85	BH	13	35 ± 9	M,F	24	jogging	daily	10-30	?
Seals and Realing (1991)	86	H	11C,13E	61 ± 2 (SE)	M,F	28	walking	3-4	30-50	40-50% heart rate reserve
		H	8C,10E	62 ± 3 (SE)	M,F	58	walking	3-4	30-60	40-50% heart rate reserve
Blumenthal (1991)	87	H	23C,35S, 41E	45 ± 8	M,F	24	walking/ jogging	3	35	≥ 70% VO _{2max}
Marceau (1993)	88	H	9	43 ± 2 (SE)	M,F	10	bicycle	3	30-45	50% VO _{2max}
		H	9	43 ± 2 (SE)	M,F	10	bicycle	3	30-45	70% VO _{2max}

Table organized according to date of publication. Abbreviations: N, normotensive; BH, borderline hypertensive; H, hypertensive; C, control; E, exercise trained; S, strength/flexibility trained; M, male; F, female; VO_{2max}, maximal oxygen consumption; ?, not available; SE, standard error

Table 3b. Effects of training on resting and ambulatory blood pressure. Longitudinal controlled studies. *Results*

Investigator	Ref.	BP at rest (mmHg)		Ambulatory BP (mmHg)						$\Delta\text{VO}_{2\text{max}}$ (%)	Δ body mass (%)	Comment
		Δ SBP	Δ DBP	Δ SBP			Δ DBP					
				day	night	24 h	day	night	24 h			
Van Hoof (1989)	83	-4	-5*	-2	+2	?	-5*	-1	?	+14*	-2*	Measurements between 6 and 8 AM, and 8 and 12 PM not used in analysis.
Gilders (1989)	84	n.c. n.c.	n.c. n.c.	-1 -3	0 -9	-1 -5	+2 +1	+4 -2	+3 -2	+10 +14*	↓* n.c.	Training period of 16 wks compared to control and 12 wks deconditioning period. Hypertensive subjects had DBP ≥ 85 and < 104 mmHg.
Somers (1991)	85	-10*	-6*	-5*	+6	?	-8*	+2	?	?	n.c.	ABP measured intra-arterially in 10 patients. Sleeping values (n=6). Six subjects studied after training and detraining for 4 months.
Seals and Realing (1991)	86	-1 -2	-1 -2	-2 -6*	-1 -6	-2 -6*	0 -2	+1 -2	+1 -1	+6* +10*	n.c. -2*	Study with non-exercising controls. Eight subjects continued exercising after 6 months at higher intensity. Control and trained subjects showed equal decreases in casual BP.

Table 3b. Continued

Investigator	Ref.	BP at rest (mmHg)		Ambulatory BP (mmHg)						ΔVO_{2max} (%)	Δ body mass (%)	Comment
		Δ SBP	Δ DBP	Δ SBP		Δ DBP		24 h				
				day	night	day	night	day	night			
Blumenthal (1991)	87	0	-1	+1	?	?	?	?	?	+14*	n.c.	Study with non-exercising controls and subjects performing a strength/flexibility program for 4 months.
Marceau (1993)	88	+1 +3	-1 +3	-6*	-2	-2	-2	-5*	-3	+4 +14*	n.c. ↓*	Latin square design with sedentary period and low and moderate intensity training program.

Table organized according to date of publication. Abbreviations: Δ , difference following training; * $p < 0.05$; ?, not measured or available; n.c., not significantly changed, data not available; ↓, significant decrease

result of starting from an already lower BP at rest or may be a function of exercising at a lower relative exercise intensity.

The blood pressure of normotensive subjects was found unchanged or decreased after training, when measured at the same absolute submaximal workload, but was usually not affected at the same relative workload (67). In hypertensive patients, most but not all studies found a significant decrease in BP at absolute workloads (67). So far, one training study in hypertensive subjects (68) has reported a significant decrease (17/12 mmHg) in exercise BP when measured at a similar relative workload.

In summary, endurance training lowers BP at rest and during exercise in hypertensive subjects, whereas in normotensive subjects the blood pressure lowering effect is rather small. Studies on the effect of endurance training on 24-hour BP are inconclusive. However, the majority of these studies seem to indicate that night-time BP is not lowered.

1.3 Possible mechanisms for the hypotensive effect of exercise training - Hemodynamic effects

It is obvious that if a reduction in BP at rest takes place in response to training, there has to be a concomitant decrease in cardiac output (CO) and/or total peripheral resistance (TPR). Thus far, exercise studies have not provided an unanimous picture of which factors are changed by training, and it is not inconceivable that different results are accounted for by differences in measurement techniques (direct vs. indirect measurement of CO) or differences in study populations: normotensives, hypertensives of various age groups with different hemodynamic profiles (borderline hypertensives vs. established hypertensives).

In studies with normotensives that reported a decrease in resting BP, not only an increase in CO with a decrease in TPR has been found (71, 73, 90), but also a drop in CO with an increase in TPR (91) or an unchanged CO with a decrease in TPR (92).

To date, seven studies in hypertensive humans have been published (69, 72, 74, 86, 93-95) that all found a reduction in resting BP and presented data on CO and TPR. In hypertensive adolescents (93), no consistent hemodynamic changes were found with training to account for the reductions in BP, except in subjects who initially had an elevated cardiac output. They showed a significant decrease in CO as a result of significant decreases in both heart rate and stroke volume. In middle-aged subjects with mild hypertension (95), low or moderate intensity training lowered SBP and DBP significantly, but changes in CO or TPR were not statistically significant. Urata et al (74) found that 10 weeks of low intensity training reduced mean BP significantly in middle-aged mild hypertensive subjects, but only a tendency for a reduction in CO was found while TPR was unaltered. However, whole blood volume and plasma volume were significantly lower. Kinoshita et al (94), applying the

same protocol in patients with mild hypertension, found a reduction in BP with a significant decrease in cardiac index as well as in plasma volume, whereas TPR index was unchanged. Nelson and co-workers (72) found a reduction in mean BP accompanied by an increase in CO in trained middle-aged hypertensive subjects, so the entire reduction in BP was due to a decreased TPR.

In older subjects with mild diastolic hypertension (86), 6 months of low intensity training lowered mean resting BP and a small but significant reduction in HR and CO was found, while stroke volume and TPR were unaltered. It was concluded that this reduction in BP was merely mediated by bradycardia-evoked reductions in CO.

Nine months of low or moderate intensity training lowered mean BP significantly in older hypertensives (69). Training resulted in a somewhat lower CO at rest and an unchanged TPR in the low intensity group, whereas TPR decreased slightly and CO was unaltered in the moderate intensity group.

1.3.1 Mechanisms for a reduction in cardiac output

Endurance training is marked by resting bradycardia and increased stroke volume at rest in normal subjects (96). Training increases parasympathetic activity to the heart with a concomitant reduction in resting sympathetic activity (96). In borderline hypertensives, a large proportion of the subjects have high CO values, due to both a larger SV and a higher HR (97). This usually is associated with an increased cardiac sympathetic drive and a decreased parasympathetic tone (97). Possibly this can be opposed by training since in hypertensive adolescents with high CO at rest, exercise reduces CO by a decrease in HR and SV (93). Furthermore, the low baroreflex sensitivity in borderline hypertensives can increase with endurance training (85). Some authors (85, 88) suggest that this mechanism could, at least partially, explain the antihypertensive action of training during daily activities. In older men and women with mild diastolic hypertension (69, 86), low-intensity aerobic training lowered BP solely by bradycardia-evoked reductions in cardiac output. However, other investigators (74, 94) did not find a heart rate reduction by low-intensity training in middle-aged hypertensives, despite a significant decrease in BP. In these studies the reduction in cardiac output was associated with a decrease in plasma volume, probably because the subjects were volume-dependent hypertensives, i.e. characterized by high cardiac indices, high serum sodium potassium ratios and low total peripheral resistances. In contrast, Nelson and co-workers, studying the effect of endurance training in middle-aged hypertensives (72), found an increase in CO accompanied by an increase in SV and reduction in HR. They suggested this could be due to an increase in preload to the heart, caused by plasma volume expansion, usually seen following endurance training in normotensive sedentary subjects (98).

1.3.2 *Mechanisms for an exercise-related reduction in peripheral resistance*

Most training studies in normal and hypertensive subjects have focussed on a reduced peripheral resistance to explain the hypotensive effect of exercise because CO at rest is usually normal and increased vascular resistance is the hemodynamic characteristic of established hypertension (99).

One of the possible mechanisms underlying the fall in TPR is an increase in cross-sectional area of the vasculature in trained muscles, secondary to an increase in local muscle mass. Increased capillary density (100), capillary to muscle fiber ratio (101) and an increase in maximal muscle blood flow (102) with training have been reported. Physical training increases the capacity for vasodilation in active limbs, probably due to adaptive changes at the arteriolar level (103, 104). The extent to which these changes relate to changes in the resistance vasculature and affect resting TPR is at present unknown.

The diameter of the arterioles can change due to vasoconstrictor and dilator influences on vascular tone. The two main mediators of vasoconstriction are the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), but other vasoactive hormones may also be involved.

[1] In training studies, plasma catecholamine concentrations have been used by most investigators as an index of SNS activity and a common finding is a decrease in plasma norepinephrine (NE) after training (71-74, 94, 95, 105, 106). In both normotensives and hypertensives, plasma NE fell after training (71-73), although in older hypertensives (69) and adolescents with hypertension (93), it did not. It was reported that the higher the baseline plasma NE, the greater the fall in BP at rest (105). A good correlation was found between changes in plasma NE and mean blood pressure following training (74). However, in borderline hypertensives, where the higher BP levels are usually associated with an increased sympathetic activity, changes in plasma NE were small and inconsistent (89). Platelet NE was decreased after training which may reflect a decreased long-term activity of SNS (107).

Total resting NE spill-over rate to the plasma provides a measure of whole body average sympathetic neural activity (108). This parameter was found greatly reduced in normal subjects after training (71). The majority (66%) of the reduction in spill-over of NE to the plasma was accounted for by a fall in renal NE spill-over whereas no change in cardiac spill-over was found (90).

Because one third of the reduction in total NE spill-over occurred outside the kidney, other regional sympathetic outflows must be involved. Studies in borderline hypertensives (109) have shown that an acute post-exercise hypotension is probably caused by sympatho-inhibition of the muscle nerves as can be measured by microneurographic techniques (109). Furthermore, using the same technique, training markedly reduced sympathetic peroneal nerve activity in normal subjects (110). Although the reduction in NE spill-over is largely seen in the kidneys, the increase in total peripheral conductance seen after training was for only 18% explained by an increase in renal vascular conductance (90). Probably the fall in TPR can be mediated by modification of

other regulatory functions of the sympathetic renal nerve through renin release and/or sodium reabsorption. Although studies suggest that a reduction in SNS activity with training is related to a BP reduction, the time course of the effect on BP appears to be more rapid than the changes in plasma NE (73).

Detraining of subjects showed a gradual increase in BP that was paralleled by a gradual increase in plasma NE, which suggests that the reduction in SNS activity may help to maintain BP at relatively low levels for some time after training (73).

Whether training can alter the sensitivity of the adrenergic system is still a matter of debate and studies are inconclusive both in humans (111) and animals (112, 113). Pressor response to NE infusions was found to be blunted after training (114). In healthy subjects, a variation of responses to endurance training with respect to beta-adrenergic receptor density has been observed. Beta-receptor density has been shown to decrease (115) or not to change (116) in lymphocytes, to increase in leukocytes (117), and to be unchanged in skeletal muscle (118). Probably beta-adrenergic responses to endurance training are tissue-specific (119). Training studies on the possibility of receptor down-regulation in hypertensive subjects have not been reported.

[2] Changes in the renin-angiotensin-aldosterone system could be an important underlying mechanism through their effect on blood volume and through the potent directly acting vasoconstrictor angiotensin II which also potentiates NE release. In young healthy subjects, an inverse relationship was reported between VO_{2max} and plasma renin activity (PRA) at rest (120). Compared to non-trained subjects lower PRA levels were found in well-trained subjects (121). In normotensive subjects, resting supine PRA was unaltered after 4 weeks of training (71) or found to be significantly reduced after 5 months of training (122). Resting plasma angiotensin II was unchanged (123) or increased (124) with training whereas plasma or urinary aldosterone was lower (125), unchanged (122) or higher (124).

In trained subjects, PRA (122, 123) and plasma angiotensin II (123) were lower during graded exercise. At a similar relative workload, PRA was unchanged after training (126). In hypertensive subjects, training did not change resting PRA, angiotensin II and plasma aldosterone in a series of studies by the same group (127). Some studies (69, 106) seem to indicate that hypertensive subjects with low PRA exhibited a larger reduction in BP than hypertensive subjects with high or normal PRA.

[3] Other hormones have been postulated to explain the BP lowering effect of regular exercise, either through a direct effect or by inhibiting NE release from nerve terminals. Atrial natriuretic peptides (ANP) are released from cardiac atria, predominantly by atrial stretch. ANP has a role in cardiovascular homeostasis by its diuretic, natriuretic and vasodilating effects. ANP has an inhibitory effect on NE stimulated vasoconstriction (128), depresses the release of renin (129) and counteracts the vasoconstrictor activity of angioten-

sin II (130). It promotes diuresis and natriuresis, possibly by inhibition of aldosterone or vasopressin (131).

Endurance training is thought to result in expansion of blood and plasma volumes (132) and it is possible that this will result in a higher density of ANP atrial granules and higher plasma ANP levels. To date only few published data are available on the effect of exercise training on ANP in humans. Similar resting ANP values were found when moderately trained young runners were compared to untrained (133) and a training break of 3 weeks in endurance runners did not alter resting ANP (134). During exercise, central blood volume rises and higher ANP levels were found, related to the absolute workload (133). In the normotensive rat model, an increase in resting ANP was observed with training, whereas atrial tissue ANP was not altered (135). However BP was not changed. In mild hypertensive subjects, slightly elevated (136) or unchanged (137) resting ANP levels were found compared to normotensive subjects. Low intensity training in middle-aged hypertensives did not change plasma ANP at rest (138).

Prostaglandin E, originating from the kidney or the skeletal muscle (139), could increase sodium secretion from the kidney and thus reduce plasma volume. Prostaglandin E concentrations at rest were found to be two to three times higher after training in hypertensive subjects (106). This could explain the volume depleting effects of physical training observed by some investigators (74) without alteration in the RAAS. In addition, prostaglandin E may cause local vasodilation in the skeletal muscle (139) or inhibit nerve NE release (140).

An important role for insulin in BP control has been postulated. Hyperinsulinemia could elevate BP by its direct effect on renal sodium retention (141) or by releasing NE, the latter resulting in arterial smooth muscle contraction and renal sodium retention (142). Endurance trained subjects have lower plasma levels of insulin and an increased sensitivity to the peripheral actions of insulin (62, 143). Insulin sensitivity rose with endurance training in normal subjects independent of body mass changes (71). Higher levels of insulin have usually been found in sedentary obese hypertensive individuals (144) and Björntorp (145) observed a fall in BP in association with a reduction in plasma insulin in obese patients after training. Whether endurance exercise can lower BP in association with lower insulin levels in non-obese hypertensives independent of a body mass reduction, warrants further research.

Several other humoral factors may play a role either by inhibiting the release of NE at sympathetic nerve endings or promoting NE uptake (see for review 127).

Finally, endothelium-derived relaxing factor is an endogenous vasodilator released by the vascular endothelium. Recent animal studies (146, 147) suggest that chronic exercise enhances endothelium-mediated vasodilation.

In summary, the mechanisms underlying the hypotensive action of regular exercise are still poorly understood. Studies on hemodynamics are controversial. The antihypertensive mechanism of exercise may be multifactorial and most probably involves suppression of sympathetic activity.

1.4 Effect of chronic exercise on the heart and vessels

The majority of ill effects of hypertension and atherosclerosis become manifest in the heart and large vessels. Hypertension is often accompanied with or preceded by changes in cardiac function or structure (148), which considerably increase the risk of morbidity. Furthermore, both components of vascular impedance, i.e. increased resistance and decreased compliance, are affected. So, the potentials of endurance exercise to oppose these changes, beside its effects on blood pressure and other risk factors, are of interest.

1.4.1 Heart

Physical conditioning results in a decrease in heart rate at rest and during submaximal workloads, while stroke volume is increased. $VO_{2\max}$ and maximal CO are increased, while peripheral changes result in enhanced maximal arterio-venous oxygen differences (96, 149). As a result training reduces cardiac work in proportion to total body work.

When athletes engaged in endurance type of exercise are compared to non-trained subjects, increased left ventricular mass (LVM) is found (150). Athletes have a larger end-diastolic left ventricular internal diameter (150, 151) and increased posterior and septal wall thickness (150, 151). The ratio of wall thickness to internal radius of the left ventricular cavity is not different from that in untrained persons (152, 153) or slightly increased (150). The ratio of septal to posterior wall thickness is not different in athletes and non-athletes (150, 151).

Training studies showed a significant increase in LVM and posterior and septal wall thickness after 4-16 weeks without a change in cavity size, when moderate exercise was performed (154, 155). In response to vigorous training, the end-diastolic internal diameter of the LV was already increased after one week, whereas changes in wall thickness occurred more gradually (156). Some authors (157) have reported increased end-diastolic dimensions without a change in LVM or wall thickness. Systolic and diastolic function of the left ventricle has usually been found to be in the normal range for athletes (158) or was unchanged after endurance training in sedentary subjects (155-157).

Changes in cardiac structure with endurance training are often referred to as eccentric LVH, because LV internal diameter increases with a proportional increase in wall thickness; this in contrast to the LVH seen in hypertension which is more concentric and marked by excessive wall thickness. In unselected groups of patients with essential hypertension, LVH is found in approximately 12% of the borderlines (159) and 15-20% of the mild to

moderate hypertensives (160). Hypertensives with increased LVM have nearly 3 times as many morbid cardiovascular events than those without (161). The correlation between LVM and casual or clinical BP is rather poor (162) and is usually only slightly better for ambulatory measurements (163). Although not commonly observed (80), some investigators suggest that night time SBP correlates the best with LVM (160); this is of particular interest since endurance training does not appear to lower BP at night (84, 86, 87). The expected reduction in BP after endurance training in hypertensives (41) could be counteracted by an increase in LVM, due to chronic intermittent overload of the heart by this type of training. A change away from concentric LVH and towards eccentric hypertrophy was found after one year of physical training in hypertensive humans (75). In this study, mean BP was significantly reduced at rest, LV cavity diameter increased significantly, whereas average wall thickness was reduced and LVM was unchanged.

Sixteen months of training in mild hypertensives on a low sodium diet (164) decreased both BP at rest and at maximal exercise, with only a tendency for LVM reduction. When LVM, however, was indexed for body mass (LVMI), no change was seen. No significant correlations between BP changes and changes in LVM or LVMI were found. On the contrary, in hypertensives, a decrease in LVMI was found after 4 months of training, without a decrease in BP at rest or during exercise, nor in 24-hour BP (165). This suggests that a reduction in LVM by training can occur independently of changes in BP, possibly via the involvement of the adrenergic system (166). In hypertension, the diastolic function is often abnormal and usually seen before LVH is obvious (167). It reflects reduced left ventricular compliance (168) or relaxation abnormalities (169). Changes or an improvement of cardiac function in hypertensive humans have not been reported, following endurance training (75, 164). In hypertensive rats, training did not change diastolic cardiac function (170) or improved it (171).

In human studies, direct evidence for an increase in the coronary collateral circulation by training is lacking (172). Possibly a decreased propensity towards arrhythmias may be a product of long-term training since an increased threshold for ventricular fibrillation in the isolated trained rat heart was found (173).

1.4.2 Vessels

Established hypertension is nearly always characterized by an elevated mean arterial BP and elevated total peripheral vascular resistance. Arterioles and in certain tissues (skeletal muscle, intestines), also muscular arteries contribute to the elevated vascular resistance (174). Proposed mechanisms underlying the overall increased vascular resistance in hypertension are (a) a decrease in the number of arterioles and capillaries, (b) decreased internal diameter of arterioles and small arteries, and (c) increase in arterial and arteriolar wall mass (174). Changes in vascular smooth muscle itself like increased sensitivity

to vasoconstrictor stimuli and a diminished relaxation process contribute to increased resistance (175).

As discussed above, most training studies have been focussed on factors that influence resistance on a functional basis, i.e. studying predominantly the remote control systems (autonomic nervous system, circulating hormones) in relation to functional vascular diameter regulation. Few studies have addressed the ability of endurance training to remodel the vascular tree. Remodeling could be achieved by chronic change in number of parallel vessels, vascular diameter or wall thickness.

In humans, endurance training can induce capillary growth in active skeletal muscles, if performed for a sufficiently long time (minimum 8 wks) (100-102). This growth is predominantly seen in the vicinity of slow oxidative fibers. As suggested by Hudlicka (176), capillary growth in skeletal muscles is probably initiated by increased blood flow. Increased shear stress in capillaries in skeletal muscle can initiate capillary growth by producing a disturbance of the luminal side of the endothelium. The involvement of growth factors has recently been suggested in endurance-trained rats (177). Whether endurance training induces growth of arterioles in human skeletal muscle is not clear. In rat models, an increase in number of small arterioles in skeletal muscle has been demonstrated, following endurance training (178). Furthermore, an increase in passive diameter of large arteries was shown. In humans, minimal vascular resistance is usually assessed by indirect measurement of limb flow (calf, forearm) by plethysmography at maximal vasodilation. In hypertensive subjects (179), borderline hypertensives (180), and even in normotensive young men with a parental history of hypertension (181), minimal vascular resistance has found to be increased during maximal vasodilation compared to age-matched normotensives. These physiological observations provide indirect evidence for the existence of the afore-mentioned structural abnormalities in hypertension. Physical training increases the capacity for maximal vasodilation in active limbs (104, 182) in normal subjects. Whether endurance training can induce regression of structural changes in hypertensive humans in various vascular beds has not been studied. It is known from antihypertensive treatment with different pharmacological agents that structural changes can be reversed in animal models of hypertension and it is evident from these studies that control of BP is not enough to achieve regression (183) and that trophic factors (catecholamines, angiotensin II, insulin) must be favorably altered (184). Reversibility of structural changes depends on the duration of hypertension (183). In man, only prolonged treatment with pindolol, captopril and nitrendipine for at least 6 months has convincingly shown to reduce minimal vascular resistance in the forearm vascular bed (185, 186).

Large vessels

Visco-elastic properties of the arterial wall enable large arteries to store to the volume of blood ejected from the heart during cardiac contraction, and to drain this volume during diastole (187). While an increase in vascular resistance causes a proportional elevation of mean BP (and thus SBP and DBP), a reduction in the visco-elastic properties of the arterial wall causes an increase in pulse pressure resulting in an increase in SBP in combination with a decrease in DBP, without a change in mean BP (188).

Several investigations have suggested that increased pulse pressure may be an important risk factor in subjects with hypertension and relates well to increased LVM in hypertensives with similar mean BP (189, 190). Furthermore, since cardiovascular morbidity and mortality of hypertensives is mainly related to disease of the large arteries, evaluation of cardiovascular risk could be more suitably done by indexes of arterial disease (191). An adequate quantification of the visco-elastic properties of the large arteries can be made by evaluating compliance and distensibility in a given artery. Arterial compliance is defined as the product of arterial volume by distensibility of the artery. Distensibility is evaluated either from the measurement of pulse wave velocity over a given arterial tract (187) or can be measured locally by the related displacement of the arterial walls per unit of pressure (192). Pulse wave velocity correlates strongly and positively with SBP measured by ambulatory monitoring (191).

Several studies have shown that arterial compliance and distensibility of the large arteries are significantly reduced with age (193) and (borderline) hypertension (194, 195). The changes may be due to structural changes, to particular responses of arterial smooth muscle tone or to a combination of both (196, 197).

It has been recognized that different antihypertensive drugs have different effects on large artery compliance, despite of equal reductions in mean BP (198). Calcium antagonists, ACE-inhibitors and some beta-1 selective beta-blockers improve large artery compliance, while some diuretics and non-selective beta-blockers do not (198). Because these conclusions are based on acute or short-term chronic studies, it is likely that this reflects functional changes rather than structural changes. Whether structural changes resulting in a decrease in compliance can be reversed is not known at present (198).

It has been suggested that an increased distensibility of large arteries will decrease the load on the vessel wall and thus may prevent accelerated aging of the vessels and maybe also atherosclerotic disease (199). Increased compliance might result in a smaller afterload for the heart, and as a consequence, help to prevent cardiac hypertrophy (199).

It would be of particular interest to know whether endurance training can improve compliance and distensibility of large arteries in normotensive and hypertensive subjects and thus reduce pulsatile stress on heart and vessels.

In a recent study (200), regional aortic compliance was measured by magnetic resonance imaging and endurance athletes were compared to age-matched healthy volunteers. Aortic compliance was found to be negatively related to age and was significantly higher in athletes. A strong negative relation was found between physical working capacity and pulse wave velocity over the carotid-femoral tract in young men (201), which suggests a positive relationship between physical fitness and arterial distensibility. An increased compliance and diameter was found in the radial artery of the dominant arm of hammer throwers compared to sedentary controls (202). The effect of 4 weeks of endurance exercise on regional arterial (aortic) compliance was studied in 7 sedentary males (203). A significant increase in arterial compliance was noticed with a significant fall in SBP. It was suggested that pressure-independent factors could contribute to the improvement (203).

The morphology of systemic arteries following endurance training has been studied in animal models. In trained rats, medial wall thickness was significantly greater in large arteries, whereas number of smooth muscle cells and lumen diameter were unchanged (204). It was suggested that this would lead to a decrease in tangential wall stress at rest. Training in hypertensive rats (205) resulted in a reduction of wall-to-lumen ratio in several large arteries (descending aorta, iliac artery, femoral artery). The trained rats had similar wall thickness values as non-trained hypertensive animals, but larger lumen diameter.

In overview, more studies are needed to establish the remodeling effects of regular exercise on the vascular tree in normotensive and hypertensive populations.

1.5 Exercise stress testing in blood pressure evaluation

In clinical practice, routine measurements of BP during exercise are mainly performed to detect an inadequate BP rise as can be due to aortic valve disease or left ventricular impairment. A decrease of SBP during exercise below the usual resting SBP or a limited (10 mmHg) increase in SBP in patients with suspected or clinically severe cardiovascular disease is a reason to terminate stress testing because of a high likelihood of post-exertional ventricular fibrillation (206).

A limited increase in SBP in normal healthy persons may not be serious in the early stages of stress testing because it may reflect anxiety-induced hypertension (207). Although an excessive rise in SBP (well over 200 mmHg) is a reason to stop exercise in some centers, complications related to high exercise SBP have never been seen (207).

The so-called double product, or SBP multiplied by heart rate, is often used in clinical and/or pharmacological studies because it provides an excellent index of myocardial oxygen consumption (208). Several investigators (see for review 209) have addressed the question whether exercise (systolic) BP is a

better predictor of target organ damage or cardiovascular morbidity or mortality than resting BP. Most studies found no significant and independent contribution of exercise BP to the variance of left ventricular mass when adjustments were made for potential confounders such as resting BP, age, height, weight and aerobic power. The exercise-induced change in SBP from baseline to a work load of 164 W was found an independent predictor of cardiovascular mortality in a study of healthy male subjects (210). In contrast in hypertensive subjects, Fagard and colleagues (211) found exercise BP not to be an independent predictor of mortality or incidence of cardiovascular events.

1.5.1 Excessive blood pressure response during exercise as a predictor of future hypertension

Numerous studies have tried to identify markers for the development of hypertension. In Western society, age, body mass, resting HR and BP have been found to be predictors (212). Laboratory predictors, such as cationic transporters and hormones, especially insulin, have been suggested (212).

In recent years, an excessive rise in BP during exercise has been proposed as a predictor of future hypertension (213-217). Wilson and Meyer (213) retrospectively analyzed the blood pressure profiles of 3395 men and 425 women who attended their clinic two times or more. After an average follow-up time of 32 months, subjects with a normal resting BP ($< 140/90$ mmHg) but with an exaggerated BP response during exercise ($> 225/90$ mmHg) at first visit were compared to subjects with a normal resting and exercise BP. The incidence of subsequent hypertension was for the subjects with exaggerated exercise response 2.38 (relative risk) times greater. Dlin et al (215) examined two matched groups of normotensive young adults. The only differentiating variable was the high BP during exercise ($< \text{or} > 200/100$ mmHg). After 5.8 years of follow-up, the group with the higher BP response had a 11.6% higher incidence of hypertension. In general, the prevalence of hypertension on follow-up among normotensive subjects with an exaggerated response to exercise testing is 2.1 to 3.4 times higher than among subjects with a normal response (216). Sensitivity of an exaggerated response to exercise for future hypertension varied for studies between 16 and 60% and specificity between 53 and 95%. However, the predictive value is limited since 38 to 89% of those with an exaggerated response to exercise did not have hypertension on follow-up (0.5-15 yr) and a normal response only marginally reduced the risk of hypertension. A common point of critic on most of these studies is the absence of standardization of the employed exercise protocols and different definitions of an exaggerated BP response. Further research should define a cut-off point separating normal from abnormal response according to age, sex and physical fitness (216), and must not only consider the absolute value of BP response but also the magnitude of BP change at each workload and establish norms that include race, sex, body mass and fitness levels. For testing pur-

poses, the use of bicycle ergometry should be favored and more studies are needed on the acute BP response to exercise in women (41).

The mechanisms behind an exaggerated BP response to exercise are poorly understood. Both an impaired capacity for exercise-induced vasodilation and an increased CO have been suggested. Alternatively, one could speculate that it is related to a low baroreflex sensitivity or a decreased arterial compliance. Wilson et al (218) compared normotensive young men with normal BP responses to exercise with normotensive men with exaggerated BP responses ($> 230/110$ mmHg) and a positive parental history of hypertension. A third group of normotensive normal responders with a positive parental history was formed. All three groups had equivalent cardiovascular parameters at rest and CO increased similarly during exercise. The group of exaggerated responders with a positive parental history showed a blunting in peripheral resistance decline during exercise. Iskandrian and Heo (219) studied normotensive subjects, with and without an exaggerated SBP response to exercise (> 200 mmHg) and patients with uncomplicated essential hypertension. Compared to the normal subjects exaggerated responders differed only with regard to a higher cardiac index and SBP during exercise. Compared to the hypertensives, exaggerated responders had a higher exercise HR, SBP, cardiac index, and left ventricular ejection fraction and lower total vascular resistance and end-systolic volume during exercise. Gottdiener and colleagues (220) compared cardiac findings in groups of sedentary normotensive men who did or did not have exaggerated elevation of SBP during treadmill exercise ($<$ or ≥ 210 mmHg). Men with exaggerated SBP during exercise had significantly elevated left ventricular mass.

1.5.2 Exercise testing in assessment of hypertension

Some studies strongly suggest that the assessment of BP during ergometric testing is quite useful in distinguishing between "true" normotensive, borderline hypertensive and hypertensive subjects (221, 222). Hypertensive patients were characterized by a rise in diastolic BP during submaximal exercise, whereas diastolic BP remained unchanged or showed only a slight increase in normotensive subjects (221, 222). This different hemodynamic pattern can be explained by the inability of hypertensive patients to reduce peripheral resistance to the same extent as normotensive subjects (223). Franz (221) studied a group of male subjects with borderline hypertension at rest (SBP: 140-160 mmHg; DBP: 90-95 mmHg). Subjects with BP of more than 200/100 mmHg at 100 watt and BP of more than 140/90 mmHg after 5 min of recovery were classified as positive responders, i.e. showing a hypertensive response. These subjects did not differ in BP response to exercise from age-matched patients with established hypertension. Subjects with a negative response had the same DBP at 100 watt as normotensive subjects. In a follow-up study of the same investigator (224), 97% of the borderline hypertensives showing a hy-

pertensive response during and after exercise testing developed established hypertension under resting conditions within 4 years.

In contrast, other investigators judged that the BP response during exercise was not particularly useful as a modality for diagnosing hypertension, in young females with borderline hypertension (225), and in children with high resting BP (226). Children with a resting BP above the 95th percentile showed a similar rise in exercise SBP as the normal group (226). Although the exercise BP was significantly higher in young females with borderline hypertension, the mean change between resting and exercise SBP and DBP was not significantly different from the normal group (225). In general, it is believed that in hypertensives changes in BP during exercise resemble the normal response found in normotensive subjects; this is, hypertensives do not have a greater change in SBP from rest to exercise (225, 227, 228). Others have pointed to the fact that an excessive rise is mainly seen in hypertensives with advanced stages of disease (229).

More large sample studies are needed to test whether exercise BP is a useful modality for diagnosing hypertension and adjustments should be made for potential confounders as age, sex, weight, body fat, resting BP and physical fitness. Furthermore, both clinical and epidemiological studies (230, 231) found substantial variation in the magnitude of BP response to exercise among healthy men and women and limited data are available at present to explain this variation. Age is independently and positively associated with SBP response to exercise (231, 232), whereas obesity (Quetelet index) is positively associated with the SBP response during treadmill testing (230). In smokers SBP during exercise is higher although only for men (232). Whether gender differences exist is not clear at the moment.

1.6 Antihypertensive medication and exercise

Lifestyle modifications are frequently advised by physicians as the start of antihypertensive treatment in mildly hypertensive subjects or as an adjunctive therapy to pharmacologic treatment. Lifestyle modification includes weight reduction, moderation of dietary sodium or alcohol intake, and increased physical activity.

Dynamic physical exercise is considered beneficial for many patients with hypertension because its potential benefits include a reduction in BP and favorable effect on other cardiovascular risk factors, increased work capacity and a general sense of well-being (233). However, in many hypertensive patients regular exercise does not lower BP to normotensive levels (65) and pharmacological treatment is necessary.

In the selection of initial drug therapy many factors should be considered and basically two approaches have been suggested (49, 234). The first approach (49) emphasizes the fact that although all major classes of antihypertensive drugs are equally effective in lowering BP at rest, only diuretics and beta-

blockers have been shown to reduce cardiovascular morbidity and mortality in long-term controlled trials. Consequently, they are recommended as first choice agents, unless they are contra-indicated or unacceptable. In the second approach (234), the selection is based on the hemodynamic profile of the drug, i.e. it should reverse the hemodynamic abnormalities of hypertension by lowering the systemic vascular resistance and preserving cardiac output and perfusion. Furthermore, concomitant diseases should be taken into account, good quality of life maintained and the drugs should have no, or favorable, effects on other CHD risk factors. Consequently in this latter approach, calcium-antagonists, angiotensin-converting enzyme inhibitors and alpha-1 receptor blockers are advocated as first choice drugs.

1.6.1 Which antihypertensive drug to choose in the physically active patient?

In addition to the afore-mentioned considerations, the ideal antihypertensive agent for patients who wish to engage in physical exercise should (a) effectively lower BP during exercise, (b) reduce BP by lowering systemic vascular resistance and preserving cardiac output and organ (active muscle) perfusion during exercise, (c) not impair left ventricular function, (d) have no arrhythmogenic potential, and (e) not impair endurance performance and trainability.

Exercise blood pressure. Table 4 compares the antihypertensive effect of several classes of drugs at rest and during exercise. Although all antihypertensive agents effectively lower BP during exercise, beta-blockers reduce exercise SBP more than other classes of antihypertensive agents. This could be an advantage in those patients with very high SBP during exercise. A much more pronounced reduction in exercise HR (20-25%) is seen with beta-blockade than with other antihypertensive drugs (235). As a consequence, the so-called double product ($HR \times SBP$), and thus myocardial oxygen consumption, is considerably lowered by beta-blockade, which could be an advantage in the treatment of patients with concomitant limited coronary blood supply during exercise.

Exercise hemodynamics. Beta-blockers lower exercise BP by reducing cardiac output (5-20%), while systemic vascular resistance (SVR) is normal or slightly increased (236). Diuretics lower exercise BP by SVR reduction with preservation of cardiac output (234). Calcium-antagonists and ACE-inhibitors reduce SVR and, during long-term treatment, cardiac output during exercise is usually unaffected (234).

Left ventricular function during exercise. All classes of beta-blockers and the calcium-antagonist verapamil impair left ventricular function, while cardiac contractility is better preserved with nifedipine and diltiazem. Other antihypertensive agents have absent or negligible effects on myocardial contractility (237).

Arrhythmias during exercise. Beta-blockers and non-selective calcium-antagonists like verapamil and diltiazem have mild anti-arrhythmic properties.

Table 4. Change in resting and exercise blood pressure during chronic treatment (> 4 weeks) with antihypertensive agents in patients with essential hypertension

		Rest		Exercise	
		SBP	DBP	SBP	DBP
Non-selective beta-blockers	(n=17)	-11% (-7 to -21)	-12% (-5 to -20)	-13% (-5 to -20)	-7% (+4 to -19)
Beta-1 selective blockers	(n=16)	-10% (-5 to -20)	-12% (-4 to -20)	-15% (-7 to -24)	0% (+1 to -19)
ACE-inhibitors	(n=12)	-13% (-6 to -19)	-11% (-2 to -19)	-8% (-5 to -12)	-8% (-3 to -13)
Calcium-antagonists	(n=24)	-12% (-1 to -26)	-13% (-1 to -29)	-8% (+4 to -12)	-11% (-4 to -20)
Diuretics	(n=10)	-14% (-8 to -24)	-12% (-6 to -19)	-8% (-5 to -14)	-5% (-4 to -14)

Adapted from Van Baak (235). SBP, systolic blood pressure; DBP, diastolic blood pressure; n, number of studies. Mean percentage changes and range of studies are shown.

Table 5. Change in maximal oxygen consumption and endurance performance after administration of antihypertensive agents

	VO _{2max}		Endurance time	
Non-selective beta-blockers	(n=19)	-10% (-1 to -19)	(n=10)	-41% (-25 to -55)
Beta-1 selective blockers	(n=21)	-6% (-2 to -17)	(n=10)	-24% (-11 to -39)
ACE-inhibitors	(n=3)	0% (+2 to -2)	(n=3)	-8% (-3 and -12)
Calcium-antagonists	(n=13)	-2% (+7 to -8)	(n=2)	-11% (-7 and -16)
Diuretics	(n=7)	-7% (-1 to -17)	(n=1)	-29%

Adapted from Van Baak (235). VO_{2max}, maximal oxygen consumption; Endurance time, time until exhaustion at a constant submaximal workload; n, number of studies; both studies in hypertensive and normotensive subjects included. Duration of studies with diuretics ranged from single dose to 7 days. Values are percentage changes from control. Mean and range of studies are shown.

Diuretics could induce hypokalemia and thus increase the frequency of premature ventricular contractions at rest and during exercise (238).

Exercise performance. Table 5 summarizes the effects of several classes of antihypertensive drugs on exercise performance. Beta-blockers have a more pronounced negative effect on both maximal aerobic exercise capacity and endurance performance than most other agents. However, in almost all studies a lower endurance exercise capacity with antihypertensive treatment has been reported (235).

Trainability. Very little is known about the influence of antihypertensive medication on trainability. Some studies have shown an attenuated conditioning response with beta-blocker therapy (i.e. a negative influence on the increase of VO_{2max}) (239-241), although this is not supported by others (242, 243). Part of this inconsistency is possibly due to the fact that a training effect may become only apparent when the drug is withdrawn (244). A blockade of peripheral adaptations with training during beta-blockade has been reported (239). Beta-1 selective blockade may impair trainability to a lesser degree (245). Trainability is not impaired by calcium-antagonists like nifedipine (246) and diltiazem (247).

1.6.2 Exercise and beta-blockers with vasodilating activity: a comparison with classical beta-blocker therapy

Recently, beta-blockers with vasodilating activity have been developed (labetalol, dilevalol, carvedilol, nebivolol). Labetalol is a non-selective beta-blocker with additional (weak) alpha-1 adrenoceptor antagonist activity (248). Dilevalol, which is the RR-isomer of labetalol, combines non-selective beta-blockade with beta-2 adrenoceptor stimulation (248). Carvedilol can be characterized as a non-selective beta-blocker with an additional vasodilator component, possibly caused by alpha-1 adrenoceptor antagonist activity

Table 6. Hemodynamic effects of chronic treatment with labetalol, dilevalol and carvedilol in hypertensive patients

	Labetalol	Dilevalol	Carvedilol
<i>Rest</i>			
BP	-17%	-15%	-14%
HR	-16%	-12%	-10%
CO	-3%	-13%	-12%
SV	+16%	+1%	-3%
TPR	-14%	-10%	-3%
<i>Exercise</i>			
BP	-20%	-10%	-16%
HR	-18%	-25%	-18%
CO	-10%	-11%	-9%
SV	+10%	+8%	+6%
TPR	-11%	+5%	-5%

Based on studies 249-254. BP, mean arterial blood pressure; HR, heart rate; SV, stroke volume, CO, cardiac output; TPR, total peripheral resistance. Mean percentage changes are shown.

(248). Nebivolol is a selective beta-1 antagonist, which has an ancillary vasodilating property of unknown nature (199).

If beta-blockade and vasodilation are properly balanced, these multiple-action drugs could prove to be attractive in the treatment of physically active patients by achieving a similar BP reduction at rest and during exercise as classical beta-blockers, but in a more physiological way. This is by reducing total peripheral resistance with no or only a minor reduction in cardiac output. Possibly this would lead to no or a lesser impairment of exercise tolerance.

Hemodynamics. Table 6 summarizes studies on the hemodynamic effects of labetalol, dilevalol and carvedilol. A marked reduction in BP at rest is found with all agents, caused by a reduction in both cardiac output and total peripheral resistance. Resting heart rate is reduced to a lesser extent than usually seen during chronic treatment with selective and non-selective beta-blockers without ISA (approximately 20-25%)(249). Compared to a reduction in cardiac output of 15-20% during conventional beta-blocker therapy, vasodilating beta-blockers reduce cardiac output less, especially labetalol. All agents reduce total peripheral resistance in contrast to the classical beta-blockers which are found to increase total peripheral resistance by 15-20% during long-term treatment (234).

During exercise, the beta-1 blocking activity of the multiple-action drugs seem to become more pronounced, i.e. the reduction in heart rate. Exercise heart rate reduction during conventional beta-blockade is in the order of 20-25% (236). Exercise stroke volume is increased with labetalol, dilevalol and car-

vedilol, as usually seen with classical beta-blocker therapy (236). Cardiac output reduction with the vasodilating beta-blockers (-9 to -11%) is in the range found with classical beta-blockers (-5 to -15%)(236). During exercise total peripheral resistance is decreased during labetalol treatment, whereas changes during dilevalol and carvedilol treatment are minor. Most studies found total peripheral resistance unchanged during selective or non-selective beta-blockade (246).

At present, no data are available on regional hemodynamics during exercise with vasodilating beta-blockers. When beta-blocker administration also leads to systemic effects, i.e. a reduction of exercise cardiac output, a reduction of skeletal muscle blood flow at submaximal workloads (50-70% $\text{VO}_{2\text{max}}$) has been found (255). Although a reduced skeletal muscle blood flow has been suggested to explain the marked impairment of endurance performance during beta-blockade (Table 5), it is probably not the sole mechanism. Oxygen uptake is on the average normal in the exercising muscles during beta-blockade because of an increased oxygen extraction (255).

Metabolism during exercise. Skeletal muscle metabolism during exercise relies on liver and muscle glycogenolysis for provision of energy substrates. Beta-oxidation of free fatty acids (FFA) provides an alternative energy source, especially during prolonged submaximal exercise.

Although animal studies have shown that beta-2 receptors located in the skeletal muscle are involved in the regulation of muscle glycogenolysis during prolonged exercise (256), human studies in general show that the rate of muscle glycogen utilization is unaffected by non-selective as well as beta-1 selective blockade (257, 258). Beta-2 adrenergic stimulation may increase glucose output from the liver (259) and after beta-2 selective blockade lower blood glucose levels were found at the end of a progressive maximal exercise test (260). Blockade of liver nerve activity, however, had no effect on hepatic glucose output during exercise (261). Whether liver glycogenolysis or gluconeogenesis is impaired by beta-blockers is at the present not known and doubted by some investigators (262). In general, plasma glucose levels during exercise are unaffected by beta-blockade (236).

Lipolysis, i.e. the breakdown of triacylglycerols into glycerol and FFA, in adipose tissue *in vivo*, is regulated by adrenergic mechanisms at rest and during exercise. Alpha-adrenergic inhibitory effects modulate lipolysis at rest, whereas beta-adrenergic stimulatory effects modulate lipolysis during exercise (263). During exercise, reductions in plasma glycerol and FFA were found ranging from 0-50% after beta-blockade (236). During recovery from exhaustive exercise, however, levels were consistently found to be lower (264, 265). This decrease tends to be more pronounced after non-selective than after beta-1 selective blockade (236). Because the uptake of FFA by the active skeletal muscles depends on the plasma concentration, it could be seriously diminished under beta-blockade (255). When lipolysis is attenuated, the reduced availability of FFA during prolonged exercise might cause a shift

from fat to carbohydrate combustion, leading to a more rapid depletion of the limited carbohydrate stores in the body. This shift is suggested by studies showing a higher respiratory exchange ratio during exercise after beta-blockade (266, 267).

On average, a slight reduction of plasma lactate with beta-blockade is found during submaximal and maximal exercise (236). Consistently, increased plasma potassium levels have been found during exercise with beta-1 selective and non-selective beta-blockade (236), probably due to a reduced reuptake of potassium by inactive skeletal muscles (268).

At present, limited data on the effect of beta-blockers with vasodilating properties on metabolism during exercise are available. During prolonged treatment with labetalol (251), a significant reduction in arterial blood lactate during steady-state submaximal exercise was found. The metabolic effects of treatment with nebivolol, atenolol and placebo have been compared during and after endurance exercise in healthy volunteers (269). During recovery of endurance exercise, plasma FFA and glycerol concentrations were reduced during atenolol and nebivolol treatment as compared to placebo, although these reductions tended to be more pronounced during atenolol than during nebivolol treatment. Lactate and glucose concentrations during exercise did not differ between the three conditions. Plasma potassium concentrations during endurance exercise were significantly higher during atenolol treatment than during nebivolol and placebo treatment.

Exercise performance. One of the most noted side-effects during classical beta-blocker therapy, especially in physically active patients, is exercise-related fatigue. These complaints have been objectivated as a reduced aerobic exercise performance capacity (236). Usually a reduction in maximal aerobic power output and maximal oxygen consumption between 5 and 10% is found (235) (Table 5). Probably, the hemodynamic effects of beta-blockers play a major role in this reduction since maximal heart rate and maximal cardiac output are reduced and thus oxygen transport capacity. A positive correlation between the reduction of exercise heart rate (and thus dose of the beta-blocker) and the reduction of maximal oxygen consumption has been noted (235). Furthermore, it has been suggested that a maximal heart rate reduction below 15-20% does not significantly reduce maximal exercise capacity (270). Few studies have investigated maximal work capacity during treatment with vasodilating beta-blockers. $\text{VO}_{2\text{max}}$ was significantly reduced (-6%) during labetalol treatment for 2 weeks (250) with a concomitant decrease in maximal heart rate of 21% and maximal cardiac output of 9%. Labetalol did not significantly affect (-6%) the time to exhaustion on a progressive maximal cycle ergometer test, but $\text{VO}_{2\text{max}}$ was not measured (271). Treatment with dilevalol significantly reduced $\text{VO}_{2\text{max}}$ (-8%) (252), while maximal heart rate (-28%) and maximal cardiac output (-19%) were also reduced. Nebivolol had no effect on $\text{VO}_{2\text{max}}$ (-1%), whereas maximal heart rate decreased by 14% (269). In an uncontrolled study in healthy volunteers (272) the effect of a

2-week treatment with carvedilol was investigated. Maximal oxygen consumption was unchanged and maximal heart rate declined by 11%.

In a number of studies, the influence of beta-blockade on submaximal endurance performance has been investigated. Endurance exercise is the performance of work at a constant submaximal intensity until exhaustion. It reflects more closely normal daily sporting activity and can thus be of greater importance in clinical practice than maximal work capacity.

Endurance exercise time was found to be greatly reduced in all studies under beta-blockade, ranging from -11 to -55% (Table 5) (235). These negative effects on endurance performance tend to be more pronounced during non-selective than during beta-1 selective blockade. The reduction in submaximal endurance performance is not related to the reduction in exercise heart rate (235). In contrast to classical beta-adrenoceptor drugs, nebivolol did not decrease endurance time significantly (-6%) (269). Studies on the effect of other vasodilating beta-blockers on endurance performance have not been reported.

How beta-blockade impairs endurance performance is not clear. Although active skeletal muscle blood flow is probably reduced during submaximal steady-state exercise, oxygen delivery to the muscles is preserved by increased oxygen extraction from the blood (255). During beta-blockade a reduced extramuscular lipolysis is found (236) combined with a blockade of muscle lipolysis (257). Although the significant increase in respiratory exchange ratio in some studies is in line with the expectation that there is a shift from fat to carbohydrate combustion during endurance exercise, muscle glycogenolysis occurs at a comparable rate (257). Some investigators suggest that this apparent inability to increase the rate of glycogenolysis in the muscle is the cause of the reduced exercise capacity (257). Furthermore, a drop in plasma glucose under beta-blockade is not a consistent finding (236). Since plasma lactate is found to be slightly reduced (236), lactate accumulation in the working muscle has to be considered. In hypertensive subjects, slightly higher muscle lactate concentrations have been found after treatment with a non-selective beta-blocker, alprenolol (273). These concentrations are, however, far below those seen after maximal exercise and in healthy subjects muscle lactate accumulation was not seen up to nearly maximal exercise (262). Changes in potassium homeostasis as seen under beta-blockade could potentially decrease endurance performance by a reduction of muscle membrane potential, resulting in impaired excitability and thus contractibility (274). Interestingly, nebivolol, which did not impair endurance performance, showed similar metabolic effects as the classical beta-blockers, except for potassium concentrations which were unchanged (269).

1.7 Aims of this thesis

Physical inactivity and poor fitness can be regarded as important risk factors of hypertension and cardiovascular disease (section 1.1). Sedentary subjects, either normotensive or hypertensive, may benefit from regular exercise by the favorable influence on various risk factors for cardiovascular diseases, such as a lowering of blood pressure (section 1.1 and 1.2). It is recognized that the reduction in resting blood pressure with endurance training is rather small, especially in normotensive subjects. Ambulatory blood pressure monitoring may provide a better estimate of the real pressure load on the heart. To date, few studies have investigated the effect of endurance training on blood pressure during daily activity and at night. In chapter 2, the effect of a moderate endurance training program on basal, exercise and ambulatory blood pressure was studied in a sedentary male population with normal or slightly elevated resting blood pressure.

It is known that mortality and morbidity from hypertension are better correlated with systolic than with diastolic blood pressure, indicating an important role of pulsatile stress. Because vessel wall properties (compliance and distensibility) of large arteries are important determinants of pulsatile stress it is of interest to know whether regular exercise can improve these determinants. To answer this question, the vessel wall properties of three large arteries (the common carotid, brachial and common femoral artery) of well-trained subjects and sedentary controls were compared, using an original ultrasound echo-tracking system based on Doppler shift (chapter 3). The vessel wall properties of these same three arteries were studied after sedentary subjects were trained for 6 weeks. Because we speculated that a potential improvement of the vessel wall properties is probably rather a reflection of functional intrinsic modification than structural change, some neurohumoral parameters were studied as well (chapter 4).

On the one hand, the blood pressure response during acute exercise testing is more frequently used as a diagnostic tool in the detection of true hypertension and in normotensives an exaggerated response is regarded as a predictor of future hypertension (section 1.5). On the other hand, it is noted by some investigators that hypertensives and normotensives show similar blood pressure responses to exercise, that there is considerable interindividual variation in response and that reference values of exercise blood pressure are remarkably scarce, especially in women. Therefore, factors that could explain the variation in blood pressure response to exercise were studied in a large population sample with normal, borderline elevated, and elevated resting casual blood pressure. In chapter 5.1, this was done for men, and in chapter 5.2 for women. Furthermore, reference values were established.

Many patients with hypertension are physically active and need pharmacological treatment to control blood pressure. In the selection of drug therapy, several factors should be considered. It is preferable to choose a medication that does not interfere with exercise performance. Especially beta-

blockers have been shown to considerably reduce endurance capacity, possibly by a reduction of skeletal muscle flow during exercise and/or by an impairment of lipolysis (section 1.6). During endurance exercise, reductions in plasma glycerol and free fatty acids may or may not be seen. During recovery, reduced levels are a more consistent finding. Because these lower levels could be the consequence of an impaired performance rather than the cause, we tried to differentiate this in chapter 6.

Beta-blockers with vasodilating properties are currently increasingly available and could provide an attractive alternative in the treatment of physically active patients with hypertension because skeletal muscle blood flow during exercise could be unaltered or even enhanced, or because lipolysis is not or less impaired. At present, data on the effect of these drugs on endurance performance are scarce. In chapter 7, carvedilol a new non-selective beta-blocker with vasodilating properties was studied during exercise in hypertensive subjects. Special interest was given to the effects on endurance performance, metabolic parameters, and neurohumoral factors during exercise.

This thesis contains seven papers which have been originally written as separate manuscripts and are presented in chapter 2 to 7.

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CHAPTER 2

Effect of exercise training on ambulatory blood pressure

JAG Wijnen, MJF Kool, MA van Baak, H Kuipers, CHA de Haan, FTJ Verstappen, HAJ Struijker Boudier, and LMAB Van Bortel

Departments of Pharmacology, Human Biology, and Movement Sciences
University of Limburg, Maastricht, The Netherlands

ABSTRACT

A possible hypotensive action of regular endurance exercise in normotensive sedentary subjects still remains a matter of debate. This is partly caused by the fact that the anticipated fall in resting blood pressure is rather small and fluctuations in blood pressure during the day can be large. The benefits of ambulatory blood pressure monitoring (ABP) originate for a great deal from the fact that the repeatability on different occasions of the ambulatory blood pressure average is improved by the greater number of readings. In this context we evaluated the effect of moderate exercise training in 19 sedentary male subjects, aged 22 to 44 years, with normal or slightly elevated blood pressure. They entered a randomized cross-over study. Measurements were performed before the study, after 6 weeks of sedentary life style (S) and after 6 weeks of training (T) on a cycle ergometer 3 times a week for 45 min at 75% $\text{VO}_{2\text{max}}$. ABP was measured with a Spacelabs 90207 monitor and cardiac output at rest with echo-Doppler. Training increased $\text{VO}_{2\text{max}}$ from 3.13 ± 0.09 to 3.40 ± 0.08 l/min ($p < 0.01$). Resting heart rate decreased from 60 ± 2 to 57 ± 2 bpm at rest ($p < 0.05$). Resting blood pressure was unchanged after training. Resting stroke volume increased from 82 ± 3 to 89 ± 3 ml ($p < 0.02$). Systemic vascular resistance index was significantly decreased due to conditioning ($p < 0.05$). The 24-h means of systolic BP (S: 125 ± 4 ; T: 125 ± 4 mmHg), diastolic BP (S: 79 ± 3 ; T: 78 ± 3 mmHg) and HR (S: 73 ± 3 ; T: 72 ± 4 bpm) did not differ between the two cross-over periods. In conclusion, moderate physical training for six weeks does not lower ambulatory blood pressure, blood pressure at rest and during exercise in normotensive sedentary male subjects; this despite clear cardiac adaptations and a reduction in systemic vascular resistance.

INTRODUCTION

There is strong evidence from well controlled intervention studies, that regular isotonic exercise can reduce resting casual blood pressure in sedentary untreated hypertensive subjects (10). Reductions in blood pressure are reported with an average of 11 mmHg for systolic blood pressure and 6 mmHg for diastolic blood pressure (7). Jennings et al demonstrated that a regular exercise program can lower blood pressure to normotensive levels in untreated patients with hypertension, in 4 weeks (21) and over 1 year (13). However, in normotensive sedentary subjects, a possible hypotensive action of regular endurance exercise still remains matter of debate. In a recent consensus statement by the World Hypertension League (8) a small average decline of 4 mmHg for systolic as well for diastolic blood pressure is assumed. But recent controlled studies did not find any blood pressure lowering effect (14, 17, 26). It is suggested that in the basal state the effect of physical training on blood pressure in normotensives is small, but becomes more important during conditions of stress (26).

The benefits of ambulatory blood pressure monitoring in the assessment of the efficacy of antihypertensive drug treatment are now well established (22).

Ambulatory blood pressure measurements make it possible to achieve a 24 hour profile of blood pressure during normal daily stress and may demonstrate a blood pressure lowering effect where conventional measurements fail to detect it mainly by reducing within subject variability due to the greater number of observations available (22). Therefore, the purpose of our present study was to evaluate the effect of moderate exercise training on basal blood pressure and on blood pressure during normal daily activities in sedentary men with normal and borderline-elevated blood pressure.

SUBJECTS AND METHODS

Twenty men aged 22 to 44 years were recruited from the general population by advertising in a local newspaper. Based on 3 consecutive casual blood pressure measurements in the morning on 2 different days 13 subjects had on average blood pressure values lower than 140/90 mmHg, 6 subjects between 140/90 mmHg and 160/95 mmHg, and one subject had a blood pressure of 160/100 mmHg. All were free of overt cardiovascular disease or other medical problems as judged by questionnaire, physical examination, routine laboratory examination, resting electrocardiogram and stress testing. They were non-smokers and took no medication. Their life style and jobs were sedentary; none of the subjects was engaged in regular sport activities of more than 1 hour/week for the last two years.

Design

Each subject gave written informed consent. The protocol of the study was approved by the Ethical Committee of the University of Limburg.

Subjects entered a randomized two-way cross-over study. One group of 10 subjects continued their sedentary lifestyle for 6 weeks, followed by 6 weeks of exercise training. The other group of 10 subjects started with 6 weeks of exercise training followed by normal sedentary activity. The exercise training consisted of 45 min exercise on a cycle ergometer at 75% $\text{VO}_{2\text{max}}$ three times a week. Each session was preceded by a 5 min warming-up and completed by a 5 min cooling down. The sessions were strictly supervised and heart rate was monitored. The work load was adjusted to maintain a constant heart rate which was between 130-160 beats/min for each subject. Subjects took no medication and kept factors as physical activity, diet and weight as constant as possible during the study. Weight was measured weekly, body fat was calculated from the sum of 4 skinfolds (6), at the start and end of each period. Urine was collected for 24 hour at the start and end of each period, to determine urinary sodium excretion. In the non-training period subjects were seen in our laboratory, every week, to promote compliance with the sedentary lifestyle.

Measurements were performed at the start of the study and at the end of each 6-week period. After the training period, evaluation took place two days after the last exercise bout to avoid acute post-exercise effects (15). Measurements were performed between 9 and 12 a.m. after an overnight fast and abstinence of caffeine for at least 12 hours. Care was taken that every subject was investigated at the same time of the day for the three measurements sessions.

Measurements

Blood pressure was measured after 5 minutes in sitting position, and after 30 minutes in a supine position using a Hawksley random-zero sphygmomanometer. The mean of 3 consecutive measurements in each position was taken. All blood pressure measurements were made by the same investigator. Cardiac output at rest was measured with the subjects in left lateral recumbent position by means of echocardiography and Doppler ultrasound measurements of blood flow velocity over the aortic valve with a conventional echosystem (Ultramarkt V; ATL, Bothell, Washington, USA) after 30 minutes of supine rest.

Aortic diameter (D) was measured from a standard 2-dimensional long-axis parasternal view at the site of the aortic root with a 2.25 Mhz transducer.

The cross-sectional area (CSA) of the aortic anulus was calculated from the aortic diameter as $CSA = 0.25 \pi * D^2$. Maximal blood flow velocity in the ascending aorta was recorded from the cardiac apex with a 1.9 Mhz continuous wave transducer. The RR-interval was derived from a simultaneous recorded ECG. Heart rate (HR) was calculated as 60/RR-interval.

Evaluation of the flow velocity-time curve for each heart cycle gives an estimate of blood flow which is related to stroke volume. The area under the flow velocity curve - or the flow velocity integral (FVI) - and its corresponding RR-interval were determined off-line with built in electronic calipers. Cardiac output was computed according to the equation: $CO (l/min) = CSA (cm^2) * FVI (cm) * HR (beats/min) * 10^{-3}$. The mean of 6 heart beats was taken. The average stroke volume (ml) was calculated as $CO/HR * 1000$. In our hands, stroke volume intra- and inter-day variability, expressed as coefficient of variation, was less than 5%. Simultaneous arterial pressure was measured using a semi-automated device (Dinamap, Criticon, Tampa, USA). Mean arterial pressure (MAP) was calculated as diastolic pressure + 1/3 pulse pressure. Systemic vascular resistance index was calculated as $MAP/cardi$ ac index (CI).

Thereafter a progressive maximal cycle ergometer (Lode, Groningen, The Netherlands) test was performed. This test started with a work rate of 100 W for 5 minutes, which was increased by 30 W every 3 minutes until exhaustion. Heart rate and systolic blood pressure (sphygmomanometer) were measured at rest, and at the end of the 100 W and 160 W stage. A blood sample was obtained from an antecubital vein for determination of plasma lactate con-

centration at exhaustion. During exercise oxygen consumption and respiratory exchange ratio were measured with a Sensor Medics Horizon metabolic measurement card. Peak oxygen uptake was defined as the mean oxygen uptake during the last minute. Plasma lactate was measured by an enzymatic auto-analyzer method, urine sodium levels by flame photometry. Ambulatory blood pressure was monitored with a non-invasive automated device, Spacelabs system model 90207 (Spacelabs Inc, Redmond, Wash, USA). With this system blood pressure is measured by oscillometry. All registrations were done on a weekday and included working periods employed outside the home. The subjects were asked to keep the same day and night rhythm throughout the three measurement periods and perform their normal daily routine. Blood pressure and heart rate were recorded every 15 minutes during the day (7 a.m. to 11 p.m.) and every 30 minutes during the night (11 p.m. to 7 a.m.). Subjects were instructed to stop muscular activity and keep their arms entirely still during BP measurements. Each reading was edited by computer and was rejected if the diastolic blood pressure was less than 40 mmHg or more than 140 mmHg, systolic blood pressure less than 80 mmHg or more than 245 mmHg, pulse pressure less than 20 mmHg and heart rate less than 40 bpm or more than 150 bpm. Over a 24 hour period, for each subject 70 to 80 blood pressure values could be analyzed.

Statistical analysis

Statistical analysis was performed according to the non-parametric Koch procedure for the two-way cross-over design using the Mann-Whitney U-test (16). If appropriate, the method of Willan and Pater (28) was used. Comparative data analysis with baseline data was made by Wilcoxon m.p.s.r. Ambulatory blood pressure data were compared by one-way analysis of variance (repeated measurements) and the Bonferroni post-hoc test. A p-value < 0.05 was considered statistically significant. All data are expressed as mean $\pm$ standard error of the mean.

RESULTS

No interactions and order effects were found, except for a slight carry-over effect for VO_{2max} . Analysis according to Willan and Pater (28), however, indicated that the cross-over analysis of VO_{2max} based on the data of the two periods was a better estimate than a parallel group comparison based only on the data of the first period.

Twenty subjects entered the study, but one stopped in the training period due to lack of motivation. Due to technical failures in two subjects more than 25% of the recordings of ambulatory blood pressure after the training period were unsuccessful. The recordings of these subjects were not used in the analysis. As a consequence, data are presented for 19 subjects, except for

ambulatory blood pressure (n=17). At the start of the study, the subjects were on average 37 ± 1 years old, weighed 77 ± 2 kg, had a percentage body fat of $20 \pm 2\%$ and were 179 ± 1 cm tall. The weight and percentage body fat remained unchanged throughout the study. The 24-hour urinary excretion of sodium was 184 ± 17 mmol at the start of the study and was not significantly different after the sedentary (167 ± 17 mmol) and training period (150 ± 15 mmol).

Based on casual blood pressure measurements there were 12 normotensive subjects and 7 subjects with a (borderline) elevated blood pressure. Using the recently proposed reference values for ambulatory pressure (25), only one subject was probably hypertensive (blood pressure over 24 hours $> 139/87$ mmHg) with an average blood pressure of $139/91$ mmHg at the start of the study. Data are presented for the whole group. In addition, subanalyses of blood pressure at rest and during exercise were made in the elevated blood pressure group (n=7).

Six weeks of training increased peak oxygen uptake (VO_{2max}) by 9% ($p < 0.01$) (Table 1). Heart rate after 30 min supine rest declined from 60 ± 2 bpm after sedentary activity to 57 ± 2 bpm after endurance training ($p < 0.05$) (Fig. 1). Stroke volume increased from 82 ± 3 ml to 89 ± 3 ml ($p < 0.02$) (Fig. 2). Calculated stroke index increased from 42.2 ± 1.3 to 45.6 ± 1.4 ml/m² at rest ($p < 0.001$) and calculated cardiac index at rest increased significantly ($p < 0.05$) during training from 2.57 ± 0.09 to 2.71 ± 0.09 l/min/m². Calculated systemic vascular resistance index fell from 2875 ± 114 dyn.s.cm⁻⁵.m² at the end of the sedentary period to 2692 ± 90 dyn.s.cm⁻⁵.m² after training ($p < 0.05$) (Fig. 3).

Table 2 presents data of resting sitting and supine blood pressure measured with the Hawksley random-zero meter. As expected, values after 5 min sitting were slightly higher compared to the supine rest values. No significant changes in resting blood pressure were found at the end of 6 weeks of training. When resting blood pressure was analyzed for the subgroup with casually elevated blood pressure (n=7) no significant changes occurred either (At the end of the sedentary period $130 \pm 5/84 \pm 4$ mmHg versus at the end of the training period, $130 \pm 3/83 \pm 2$ mmHg). Heart rate in this group declined from

Table 1. Data on maximal aerobic exercise capacity (n=19).

	At start study	Sedentary period	Training period
Peak heart rate (bpm)	181 ± 3	180 ± 2	178 ± 3
Peak oxygen uptake (l/min)	3.15 ± 0.08	3.13 ± 0.09	3.40 ± 0.08 *
Peak respiratory exchange ratio	1.15 ± 0.01	1.16 ± 0.02	1.18 ± 0.01
Peak lactate (mmol/l)	11.3 ± 0.7	10.3 ± 0.6	11.8 ± 0.7

*All values are expressed as mean $\pm$ standard error. * $p < 0.01$ for difference between sedentary and training period.*

Fig. 1 Heart rate after 30 min of supine rest and during 24-hour ambulatory recording at the start of the study (B), at the end of a sedentary period of 6 weeks (S) and at the end of the training period (T). * $p < 0.05$ for differences from sedentary values.

Fig. 2 Cardiac index and stroke volume at the start of the study (B), at the end of a sedentary period of 6 weeks (S) and at the end of the training period (T). * $p < 0.05$ for differences from sedentary values.

65 ± 2 bpm to 60 ± 3 bpm ($p < 0.02$). Blood pressure and heart rate measured at rest sitting on the bicycle and during submaximal exercise are shown in Table 3. No significant changes in blood pressure were found due to the exercise training; this in contrast to a highly significant decline ($p < 0.01$) in the submaximal exercise heart rate following training. Comparable changes were observed in the elevated blood pressure group: sitting systolic blood pressure was 157 ± 4 mmHg after the sedentary period and 151 ± 6 mmHg

*Fig. 3 Systemic vascular resistance index at the start of the study (B), at the end of the sedentary (S) and at the end of the training period (T). * $p < 0.05$ for differences from sedentary values.*

Table 2. Blood pressure after 5 minutes of sitting and 30 minutes of supine rest (n=19)

	At start study	Sedentary period	Training period
<i>Sitting</i>			
SBP (mmHg)	123 ± 4	117 ± 3	120 ± 3
DBP (mmHg)	80 ± 2	78 ± 2	79 ± 2
<i>Supine</i>			
SBP (mmHg)	115 ± 2	111 ± 2	113 ± 3
DBP (mmHg)	76 ± 2	73 ± 2	73 ± 3

Means are presented ± standard error. SBP, systolic blood pressure; DBP, diastolic blood pressure. Blood pressure measured with the Hawksley random-zero meter.

after training (not significant), whereas sitting heart rate at rest was significantly decreased from 79 ± 5 bpm to 72 ± 4 bpm after training ($p < 0.05$). At a workload of 100 W, a systolic blood pressure of 192 ± 9 mmHg was found after the sedentary period and 194 ± 7 mmHg after training (n.s.); for the heart rate, these values were 124 ± 6 and 113 ± 4 bpm ($p < 0.05$).

Table 4 presents data of the ambulatory blood pressure monitoring and Fig. 4 shows the 24-hour blood pressure profile. Ambulatory blood pressure is not lowered by training, neither during 24 hours nor during the day- or night-time. There is a small, but statistically significant decline in ambulatory

Table 3. Systolic blood pressure and heart rate at rest and during submaximal exercise (n=19).

	At start study	Sedentary period	Training period
SBP at rest (mmHg)	146 ± 4	141 ± 4	141 ± 4
HR at rest (bpm)	70 ± 3	74 ± 3	71 ± 3
SBP at 100 W (mmHg)	179 ± 6	181 ± 5	177 ± 5
HR at 100 W (bpm)	118 ± 4	118 ± 3	111 ± 3*
HR at 130 W (bpm)	137 ± 4	136 ± 4	129 ± 4*
SBP at 160 W (mmHg)	201 ± 6	194 ± 6	198 ± 5
HR at 160 W (bpm)	157 ± 4	157 ± 4	145 ± 4*

At rest: sitting on the bicycle immediately before exercise. Means are presented ± standard error. SBP, systolic blood pressure; HR, heart rate. * $p < 0.01$ for differences between sedentary and training period.

Table 4. Ambulatory blood pressure and heart rate (n=17).

	At start study	Sedentary period	Training period
24 hr mean			
SBP	126 ± 4	125 ± 4	125 ± 4
DBP	80 ± 3	79 ± 3*	78 ± 3*
HR	73 ± 4	73 ± 3	72 ± 4
Daytime mean (7 a.m. - 11 p.m.)			
SBP	130 ± 3	129 ± 4	129 ± 3
DBP	83 ± 3	82 ± 3*	81 ± 3*
HR	76 ± 4	76 ± 3	75 ± 4**
Night time mean (11 p.m. - 7 a.m.)			
SBP	112 ± 3	110 ± 3	110 ± 3
DBP	67 ± 3	65 ± 3	64 ± 2
HR	62 ± 2	61 ± 2	63 ± 3*

Means are presented ± standard error. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. * $p < 0.05$ for differences from values at the start of the study; * $p < 0.05$ for differences between sedentary and training period.

diastolic blood pressure between the first (at the start of the study) recording and the recordings during the cross-over periods. Training lowered the heart rate only during the daytime ($p < 0.05$). During nighttime heart rate was even somewhat higher after training ($p < 0.05$). For the elevated casual blood pressure group, only 5 subjects had complete records and the average 24-hour blood pressure was $130 \pm 3/84 \pm 4$ mmHg for the sedentary period, and $130 \pm 5/83 \pm 2$ mmHg after training. Day- and night-time recordings were in line

Fig. 4 Circadian rhythm of systolic and diastolic blood pressure at the end of the sedentary and training period. The ambulatory blood pressure curve after training is compared with the 95% confidence limits of the ambulatory blood pressure curve in the sedentary period.

with the whole group and showed no effect of physical exercise training, while conditioning lowered the heart rate during the day ($p < 0.05$).

DISCUSSION

The anticipated fall in resting blood pressure from exercise training in sedentary normotensive subjects is small (8). An average fall of 4 mmHg for systolic as well as diastolic blood pressure must be viewed against the magnitude of the variability in blood pressure. Fluctuations of 40% in blood pressure can readily occur at random during the day (18). By using ambulatory recordings and thus increased numbers of readings, the variability between repeated blood pressure estimations is markedly reduced and smaller differences in blood pressure fall are more easily detected (4). In addition, evidence is growing that ambulatory blood pressure measurement is superior to traditional blood pressure measurements in providing a proper estimate of the real pressure load to the heart (19).

In this study a Spacelabs 90207 oscillometric blood pressure monitor was used, which has been successfully validated according to the British Hyper-

tension Society protocol (23). All but one of the subjects in this study could be classified as normotensive based on recently proposed reference values for ambulatory blood pressure, although 7 subjects had elevated casual blood pressure values at the start. This points to an additional advantage of ambulatory monitoring, namely to better differentiate between true and pseudo-hypertensives (24). It is conceivable that part of the inability to find a significant decrease in systolic blood pressure by conditioning in 11 out of 33 studies in sedentary hypertensive men (10) can be explained by misdiagnosis. Comparing the ambulatory diastolic blood pressure averages at the start with sedentary and training (pooled) averages, there is a small but significant decline. Thus, the absence of some first measurement effect cannot be ruled out (5).

The most important finding of this study, however, is the lack of any hypotensive effect, as measured with ABP, of conditioning in normotensive sedentary subjects. This is in agreement with other studies (9, 27). Gilders et al (9) studied 10 normotensive sedentary male and female subjects after a 16-week endurance exercise conditioning period (3 days/week, 30 min of exercise at 80% of maximal heart rate) and after a 12-week de-conditioning period. Although conditioning increased $\text{VO}_{2\text{max}}$ in that study by 14%, which is higher than the average 9% in the present study, blood pressure (measured with the Del Mar Pressurometer III) did not decrease, neither over 24-hours nor during the day or night. A shortcoming of the study by Gilders et al is the fixed order in which conditioning and de-conditioning periods were alternated, which cannot rule out an order effect. Using a randomized cross-over design, Van Hoof et al (27) studied 26 sedentary men who trained for 4 months (3 days/week, intensity not mentioned) or continued their sedentary lifestyle for 4 months. An increase in $\text{VO}_{2\text{max}}$ by 14% did not change the ambulatory blood pressure during the day or the night (measured by a Spacelabs 5200 device), except for the day-time diastolic blood pressure which was lowered by 5 mmHg. Average 24-hour blood pressure values were not given because measurements between 6 and 8 A.M. and 8 and 12 P.M. were excluded. The findings in the present study and afore-mentioned studies (9, 27) on ambulatory blood pressure and training are in contrast with the prevailing view that endurance training lowers blood pressure at rest in normotensive sedentary subjects (8).

We also measured casual blood pressure at rest after 5 min sitting and in a more basal state after 30 min of rest but did not find a reduction in blood pressure, despite of clear adaptive effects at rest of the heart rate, stroke volume and systemic vascular resistance to training. Jo et al (14) trained 14 untreated hypertensives and 14 normotensives for 12 weeks and observed a significant fall in blood pressure in the hypertensive group but not in the normotensives. Lightfoot et al (17), studying the effect of 10 weeks of aerobic training on lower body negative pressure responses, did not find a change in systolic and diastolic blood pressure at rest in normotensive subjects in spite

of a 20% increase in $\text{VO}_{2\text{max}}$. It is possible that the blood pressure response to training was influenced by other factors. Diet, weight and body composition were, however, not altered. It can be argued that the level of physical activity of our subjects in normal daily life was too high to see an effect of conditioning on blood pressure. Jennings et al (12) suggested that the antihypertensive effect of regular exercise is a low threshold phenomenon and the major effect occurs when sedentary subjects increase their activity level to only moderate levels. But all our subjects had white-collar jobs and did not engage in regular (endurance) sporting activities for the last 2 years. Vanhees et al (26) and Van Hoof et al (27), reporting on the same normotensive subjects, described training-induced changes varying according to the measuring conditions. They found that in the basal state (after about one hour rest in recumbent position), the effect of physical training on blood pressure in normotensive subjects is negligible (26), but becomes more important during conditions of stress. They reported a decrease in submaximal exercise blood pressure. In sharp contrast to our findings, Meredith et al (20) measured supine blood pressure after the normotensive subjects had been lying for 25 min, and found a decrease of 8 mmHg for systolic blood pressure and 5 mmHg for diastolic blood pressure after 4 weeks of training at a workload of 60-70% W_{max} . In the present study no effect of training on exercise blood pressure measured at 100 and 160 W was found despite a clear reduction in submaximal heart rate and this is in accordance with De Vries et al (5), who found no effect on blood pressure measured at 75 W in older men.

Remarkably, training induced a significant 6% increase in cardiac index. This modest rise in the resting cardiac index is in line with previous studies (11, 20), using the "indirect Fick" method, but conflicts with the study by Gilders et al (8), who measuring cardiac output with echo-Doppler, found an unaltered cardiac output at rest following conditioning. The increase in cardiac index was caused by an increase in stroke volume, which in turn is most likely to be the result of an increased preload and increased central blood volume associated with training (1). Because the mean arterial pressure was found to be unchanged by training and the cardiac index was increased, systemic vascular resistance index was consequently decreased. Afterload reduction is a crucial component of the integrated cardiovascular response to training. An increase in the size of the capillary bed of the skeletal muscle is a well-known training effect. This could in part account for the reduction, but it is believed that regulatory effects on arteriolar level are most important (2). A lot of research has focussed on a probable decline in sympathetic activity due to conditioning, but results lack consistency (10).

Although we discussed the subjects as one group, being normotensive based on their ambulatory recordings, we made analyses of the subjects with elevated casual blood pressure. A hypotensive effect of a physical exercise training could not be detected neither on resting, exercise or ambulatory blood pressure. Recently, Blumenthal and colleagues (3) assessed the effects

of a moderate physical exercise program in patients classified as mild hypertensives, based on resting blood pressure. Ambulatory blood pressure monitoring was performed using an Accutacker monitor, from 8 am until bedtime. The study was designed as a randomized controlled trial. After 4 months of exercise training (3 times a week, aerobic exercise for 35 minutes at 70%VO_{2max}) subjects in the aerobic exercise group did not exhibit greater reductions in ambulatory blood pressure than subjects in the control group.

In conclusion, this study shows that in normotensive sedentary subjects six weeks of training does not lower ambulatory blood pressure, blood pressure at rest and during exercise, despite clear cardiac adaptations and a reduction in systemic vascular resistance at rest.

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CHAPTER 3

Vessel wall properties of large arteries in trained and sedentary subjects

JAG Wijnen, H Kuipers, MJF Kool, APG Hoeks, MA van Baak, HAJ Struijker Boudier, FTJ Verstappen, and LMAB Van Bortel

Departments of Pharmacology, Physiology and Biophysics, University of Limburg, Maastricht, The Netherlands, and Institute of Sports Medicine Limburg, Maastricht, The Netherlands

Adapted from: Basic Res Cardiol 86 (suppl 1): 25-29, 1991

ABSTRACT

Vessel wall properties (distensibility and compliance) of the elastic common carotid artery and the muscular femoral and brachial arteries were studied with a dedicated ultrasound system in 15 trained male cyclists and 15 healthy sedentary males matched for age, height and weight. Simultaneously, arm blood pressure was measured with a Dinamap and heart rate and stroke index with bioimpedance electrocardiography.

Heart rate at rest was significantly lower and stroke index significantly higher in the trained subjects. Blood pressure and pulse pressure did not differ. Vessel wall properties and diameter of the common carotid artery showed no differences between the groups. Diameter of the femoral artery was significantly larger ($p < 0.05$) in cyclists and cross-sectional compliance tended to be higher. Distensibility coefficient was not different. Diameter of the brachial artery did not differ between the two groups. Cross-sectional compliance of the brachial artery was significantly higher in the cyclists ($p < 0.02$), distensibility coefficient was 22% higher ($p = 0.09$).

These results suggest that endurance training in cyclists might cause structural adaptation of the femoral artery and a more general decrease in smooth muscle tone of muscular arteries.

INTRODUCTION

Physical conditioning, especially endurance training is accompanied by various central and peripheral cardiovascular adaptations. Striking features of the training response are an increase in left ventricular end-diastolic volume of the heart, a sinus bradycardia at rest, a decreased heart rate during submaximal exercise and an increase in the size of the capillary bed of the skeletal muscle (1).

Furthermore physical training increases the capacity for vasodilation in active limbs, probably by increasing the capacity of arteriolar vessels to accommodate blood flow during exercise (2). Large arteries have a conduit and buffering function (3). They transform the systolic flow jet from the heart into a more continuous flow for tissue perfusion. Arterial distensibility and compliance are vessel-wall properties that determine, respectively, the elastic and buffering function of large arteries. Whether physical training induces changes in these properties has not been studied yet.

Recently, ultrasound techniques have been developed (4), by which these vessel-wall properties can be measured. In the present study we compared the vessel-wall properties of three large arteries i.e. the common carotid artery, the brachial artery and the common femoral artery, between endurance-trained cyclists and sedentary subjects at rest.

MATERIALS AND METHODS

Subjects

The study was performed on 15 well-trained male cyclists and 15 healthy sedentary male subjects matched for age (± 2 yr), height (± 2 cm) and body mass (± 2 kg). The cyclists had been active in competition for at least two consecutive years and measurements were taken in the second month of the training season. The sedentary subjects did not perform endurance or competitive types of sports and were mostly recruited from a student population. All subjects were free of overt cardiovascular disease, did not smoke and used no cardiovascular medication.

After 15 min of supine rest, 3 consecutive measurements of blood pressure with a Hawksley random zero meter showed a blood pressure less than 140/90 mmHg in all subjects. The protocol was approved by the institutional Ethics Committee. Informed written consent was obtained from each subject.

Methods

On the day of examination, the subjects abstained from caffeine and reported at the laboratory at least 3 hours after they had their last meal. Furthermore, no vigorous exercise was performed the day before. Body height and body mass were measured and body fat was calculated from the sum of 4 skinfolds according to Durnin and Womersley (4).

The ultrasound investigation was carried out in a quiet room ($22 \pm 1^\circ\text{C}$) after 15 min in the recumbent position. Arterial blood pressure was measured every 2 min at the left arm with a semi-automated oscillometric blood pressure device (Dinamap, Criticon, Tampa, USA). Systolic and diastolic pressures were recorded at least 6 times during the echo investigations and the average value was taken as the subject's reading.

Vessel wall properties

A 7.5 MHz ultrasound system (Ultramark-V, ATL, Bothell, Washington, USA) was used to locate subsequently the common carotid artery, the common femoral artery and brachial artery, all at the right side, whereafter the system was switched to the M-mode with M-line placed perpendicular to the axis of the vessel. For a period of 4 to 5 seconds, the radio-frequency signals received in M-mode were stored temporarily in a dedicated memory module (5), synchronous with an ECG-derived trigger for timing reference purposes. After completion of the data collection, the signals were transferred to a personal computer (PC), where the first M-line acquired was used to identify the positions of the vessel walls. Off-line Doppler processing of the radio-frequency signals within windows coinciding with both walls (Fig. 1A) reveals

Fig. 1A Radio-frequency (RF) signal with RF-DAS (5)

Fig. 1B Registration of the vessel wall movement of the common carotid artery during 5 heart cycles in a young healthy volunteer. ant: anterior wall movement; pos: posterior wall movement; dist: distension, change in diameter during the heart cycle

the displacement of the arterial walls was a function of time, while the difference between both represents the distension waveform (Fig. 1B). The coefficient of variation in the peak-to-peak distension varied from 8-13%, depending on the artery (6). This variation can (partly) be attributed to the beat-to-beat changes in local pulse pressure.

From the diameter at the onset of the cardiac cycle (D), the relative change in diameter during the cardiac cycle (distension; ΔD) and pulse pressure (ΔP , systolic minus diastolic blood pressure), distensibility coefficient (DC), and cross-sectional compliance (CC) were calculated using the following equations:

$$DC = \frac{\Delta A/A}{\Delta P} = \frac{2 (\Delta D/D)}{\Delta P}$$

$$CC = \frac{\Delta V/L}{\Delta P} = \frac{\pi D * \Delta D}{2\Delta P}$$

$\Delta A/A$: relative change in cross-sectional area of the vessel

$\Delta V/L$: change in volume per unit of length

Cardiac output measurement

Cardiac output and heart rate were continuously measured by electrical bioimpedance (NCCOM3-R7; BoMed Medical Manufacturing LTD, Irvine, California, USA). The monitor automatically averages stroke volume over 12 cardiac cycles. Recently, Northridge et al (7) compared this method to Doppler echocardiography and the thermodilution method in patients within 24 hours after acute myocardial infarction and found close agreement in most patients, and good reproducibility.

Exercise test

After the ultrasound investigations, maximal working capacity ($W_{\max}$) was assessed on a bicycle ergometer (Lode, Groningen, The Netherlands) with a progressive protocol until exhaustion (start 100 W; then 50 W increase every 3 min). Peak heart rate was obtained from ECG and blood was sampled from a cubital vein after 3 min in the recovery phase for determination of plasma lactate. Plasma lactate was determined spectrophotometrically according to the LDH method with a centrifugal analyzer (type Cobas Bio).

Data analysis

Results are presented as mean $\pm$ SEM ($n = 15$ in both groups). Comparison between the trained and sedentary subjects was made by the non-parametric Mann-Whitney U-test. A p -value less than 0.05 was considered statistically significant.

RESULTS

Subject characteristics are presented in Table 1. With regard to age, height and body mass no significant differences between the two groups existed. Trained subjects had a significantly lower percentage body fat and resting heart rate was on average 10 beats.min⁻¹ lower ($p < 0.05$). Stroke index was significantly higher. Maximal effort during the progressive maximal exercise test was comparable between the two groups as judged by maximal heart rate and peak plasma lactate concentration. A large significant difference was found in absolute maximal aerobic power ($W_{\max}$) and $W_{\max}$ standardized for body mass ($W_{\max} \cdot \text{kg}^{-1}$).

Table 1. Subject characteristics

	Sedentary	Trained
Age (y)	24.3 ± 1.0	24.4 ± 1.0
Body height (cm)	183.5 ± 1.3	182.2 ± 1.9
Body mass (kg)	74.7 ± 2.5	74.9 ± 2.1
Body fat (%)	14.3 ± 1.0	10.8 ± 1.6*
Systolic blood pressure (mmHg)	120.9 ± 2.9	117.5 ± 2.4
Diastolic blood pressure (mmHg)	68.5 ± 1.9	63.5 ± 1.1
Pulse pressure (mmHg)	52.3 ± 2.6	54.0 ± 2.0
Resting heart rate (bpm)	60.2 ± 2.1	50.0 ± 2.1*
Stroke index (ml.m ⁻²)	66.9 ± 2.9	74.8 ± 3.4*
W _{max} (W)	289.6 ± 10.4	392.2 ± 12.8*
W _{max} .kg ⁻¹ (W.kg ⁻¹)	3.91 ± 0.15	5.24 ± 0.12*
Maximal heart rate (bpm)	189.7 ± 2.6	186.1 ± 2.8
Plasma lactate (mmol.l ⁻¹)	10.9 ± 0.6	11.5 ± 0.4

* $p < 0.05$. Blood pressure measured with Dinamap in supine position.

Table 2. Arterial diameter (D), diameter change (ΔD), distensibility coefficient (DC) and cross-sectional compliance (CC) for the right common carotid artery, right common femoral artery and right brachial artery in sedentary and trained subjects

	Sedentary	Trained
Carotid artery		
D (mm)	6.37 ± 0.13	6.41 ± 0.11
ΔD (μm)	630 ± 24	669 ± 33
DC (10 ⁻³ /kPa)	29.6 ± 2.0	30.3 ± 2.9
CC (mm ² /kPa)	0.93 ± 0.05	0.97 ± 0.08
Femoral artery		
D (mm)	8.81 ± 0.18	9.89 ± 0.31*
ΔD (μm)	690 ± 43	819 ± 57
DC (10 ⁻³ /kPa)	23.4 ± 1.9	25.4 ± 3.8
CC (mm ² /kPa)	1.43 ± 0.12	1.82 ± 0.19
Brachial artery		
D (mm)	4.36 ± 0.08	4.40 ± 0.11
ΔD (μm)	409 ± 39	523 ± 35*
DC (10 ⁻³ /kPa)	27.5 ± 2.6	33.7 ± 2.5
CC (mm ² /kPa)	0.40 ± 0.03	0.51 ± 0.03*

* $p < 0.05$.

With regard to blood pressure, systolic blood pressure was not significantly different, but diastolic blood pressure tended to be lower in the trained group ($p = 0.05$). Pulse pressure did not differ.

In Table 2, vessel wall properties of the three large arteries are shown. No significant differences for the elastic common carotid artery were found. Diameter of the muscular common femoral artery was on average 12% larger in the cyclists ($p < 0.02$). Cross-sectional compliance averaged 27% higher and distensibility coefficient 9% higher, but the level of significance was not reached ($p = 0.09$ for cross-sectional compliance). Diameter of the muscular brachial artery showed no difference between the groups. Distensibility of the brachial artery tended to be higher (23%; $p = 0.09$) in the trained group. Cross-sectional compliance was 28% higher ($p < 0.02$) in the cyclists.

DISCUSSION

In this study assessment of local vessel wall properties was made by a dedicated ultrasound technique. Using this technique, it has previously been shown that distensibility and compliance of large arteries decrease with age (8), that they are lower in females than in males (9), and that arterial (border-line) hypertension is associated with a decrease in compliance and distensibility (10). Recently a diurnal pattern in vessel wall properties of large arteries has been demonstrated (11).

It has been established that in order to increase maximal cardiac output with physical training the combined effects of an improved myocardial performance and a reduced resistance to flow are needed (12). Physical training increases the capacity for vasodilation in the active muscles, probably by structural changes at the arteriolar level, and enables the trained individual to utilize a larger fraction of maximal vascular conductance than the sedentary subject (2). Literature data on the effect of physical training on large arteries are scarce. This is the first study in which vessel wall properties of large arteries were compared between endurance trained athletes and sedentary subjects.

Physical training of competitive cyclists is characterized by many hours of repeated bouts of high-intensity exercise, predominantly isotonic and performed especially with the quadriceps muscles. In addition, some work is done by the arms and upper body, mainly isometric in nature. The present study observed several differences between the vessel wall properties of the large arteries of cyclists and their sedentary counterparts, which could be the result of physical training. However, the possibility that these differences merely reflect genetic endowment cannot be ruled out. With regard to the common femoral artery, the internal diameter was found to be 12% larger in cyclists at rest. Most likely this represents a local adaptation to facilitate the large blood flow to the quadriceps muscles during strenuous exercise. It can be hypothesized that it is in part the resultant of [1] a chronic flow-dependent

vasodilation (13), [2] caused by a reduced sympathetic stimulation during exercise, [3] by other neurohumoral regulatory mechanisms or [4] simply is the consequence of volume overload.

It is not clear whether the vasodilation seen at rest is primary functional or rather structural in origin. Recently, it has been found (14) that the radial artery of the dominant arm of hammer throwers has a significantly larger diameter and increased compliance at rest, compared to the opposite arm and the arms of sedentary controls, which probably suggests a more structural adaptation. A flow-dependent vasodilation of the femoral artery at rest seems unlikely, because leg blood flow at rest is not different in endurance-trained and sedentary subjects (2). A more systemic functional component to the dilation could be imagined, however, this is not revealed by differences in the brachial diameter between the two groups.

Surprisingly, we found no differences in vessel wall properties (cross-sectional compliance and distensibility coefficient) of the femoral artery in cyclists. Distensibility coefficient of the femoral artery was not significantly different, probably as a consequence of the structurally larger diameter. An increased cross-sectional compliance could be expected since the diameter was significantly larger with an unchanged distensibility coefficient. An obvious explanation for the absence of statistical significance could be the wide dispersion of individual data.

The most interesting finding of the present study is a better cross-sectional compliance of the brachial artery in trained subjects compared to that of sedentary subjects. As described in the method section, cross-sectional compliance is related to diameter and distensibility coefficient. Because average diameter was only 1% larger in the trained group and average distensibility coefficient was 23% higher, the better cross-sectional compliance has to be considered the resultant of a better vessel wall distensibility. The better cross-sectional compliance was only observed in the muscular brachial artery and not in the more elastic common carotid artery. Therefore, it is tentative to suggest that aerobic training can induce a decrease in muscle tone of the brachial artery and perhaps also a more general decrease in muscle tone of other muscular arteries. This could be related to a reduction in sympathetic activity. Whole-body spill-over rate of norepinephrine into the plasma, a measure of average sympathetic neural activity, is significantly reduced with training (15). Whether central, peripheral or local mechanisms are primarily or secondarily responsible for this change remains to be established. A preferential effect of endurance exercise training on renal sympathetic activity has been noticed (16) and endurance training reduced sympathetic activity of the peroneal nerve assessed by microneurography (17). Alternatively, training could decrease the response to adrenergic stimulation at the level of the smooth muscle (18). The renin-angiotensin system could also play a role since in trained subjects lower levels of plasma renin have been found (15, 19). In

addition, endothelial-mediated flow-dependent changes of the arterial wall cannot be ruled out (20).

An improvement in vessel wall properties of large arteries in cyclists is in line with the observed higher regional compliance of the aorta of athletes compared to age-matched controls as measured with magnetic resonance imaging (21). A strong inverse linear relationship was found between pulse wave velocity measured over the carotid-femoral tract and physical working capacity in young men (22). This indicates a positive relation between aortic distensibility and physical working capacity. Arterial compliance is a major determinant of the afterload of the heart (23). A decrease in afterload by a decrease in vascular impedance due to an increase in arterial compliance with training could therefore improve cardiac performance (24).

Longitudinal studies are needed to find out whether training can improve vessel wall properties of large arteries in sedentary populations. If it does, it might contribute to explain why physical inactivity is associated with a higher risk of developing hypertension (25) and with a higher cardiovascular morbidity and mortality (26).

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CHAPTER 4

Vessel wall properties of large arteries and endurance training

JAG Wijnen, MJF Kool, JP Kooman, MA van Baak, AP Hoeks,
HAJ Struijker Boudier, and LMAB Van Bortel

Departments of Pharmacology, Human Biology, Internal Medicine, and
Biophysics, University of Limburg, Maastricht, The Netherlands

Adapted from: J Hypertension 11 (suppl 5): 88-89, 1993

ABSTRACT

Cross-sectional studies found a positive relation between arterial elasticity and physical working capacity, higher regional compliance of the aorta in endurance-trained athletes and better vessel wall properties of the brachial and femoral artery in cyclists compared to sedentary subjects.

In this study, it has been hypothesized that physical training might induce changes in vessel wall properties of large arteries in sedentary men. Nineteen healthy men entered a randomized two-way cross-over study, consisting of either continuation of their sedentary lifestyle for 6 weeks or 6 weeks of moderate exercise training at 75% $\text{VO}_{2\text{max}}$, 3 times a week for 45 minutes. Before and after these periods, vessel wall properties (distensibility and compliance) of the elastic common carotid artery and the muscular femoral and brachial arteries were studied with a dedicated ultrasound system. In addition, plasma catecholamines, plasma renin and plasma atrial natriuretic peptide concentrations were measured at rest.

Training increased $\text{VO}_{2\text{max}}$ from 3.13 ± 0.09 to 3.40 ± 0.08 l/min ($p < 0.01$). Resting heart rate declined significantly. Resting blood pressure was $118 \pm 2/74 \pm 2$ mmHg before and $117 \pm 3/74 \pm 2$ mmHg after training. Pulse pressure was unaltered. Diameter, distensibility coefficient and cross-sectional compliance of the three large arteries were not significantly different between the sedentary and training period. No significant changes in neurohumoral parameters were found following training.

In conclusion, a moderate exercise training program of 6 weeks does not change the vessel wall properties of large arteries in sedentary men.

INTRODUCTION

Recent training studies have provided supporting evidence for a blood pressure lowering effect of regular moderate isotonic exercise, both in normotensive (1, 2) and in hypertensive populations (3, 4). The underlying hemodynamic mechanisms, however, remain unclear; both changes in cardiac output and/or a decline in vascular resistance have been reported (5, 6).

To what extent neurohumoral changes are associated with the decrease in blood pressure also remains a matter of debate. A reduction in sympathetic nervous system activity has been a common finding (2, 3, 4), while a role of the renin-angiotensin-aldosterone system is controversial (2, 5). At present, few data are available on the effect of training on atrial natriuretic peptides (ANP). In animals, an increase in resting ANP was observed after training (6), but in humans cross-sectional comparison between sedentary and endurance-trained subjects failed to show significant differences (7).

Beside a possible decline in vascular resistance, exercise training could have an effect on another component of vascular impedance, i.e. compliance. This has been suggested by cross-sectional studies finding a positive relationship between arterial elasticity and physical working capacity in young men (8), higher regional compliance of the aorta in endurance-trained athletes vs. sedentary age-matched controls (9) and in a recent study which found cyclists

to have improved vessel wall properties of the brachial and femoral artery compared to sedentary controls (10).

Pulsatile stress in the vessel wall is substantially determined by arterial distensibility and may play a role in the onset of atherosclerosis. A decrease in compliance increases pulse pressure and left ventricular load. Distensibility and compliance are vessel wall properties which can now be measured non-invasively with ultrasound techniques (11). Distensibility and compliance have been found decreased with age (12) and hypertension (13).

An improvement by training of vessel wall properties may offset the age-related changes and the changes seen with high blood pressure and may help to explain why physically inactive persons have a higher risk of developing hypertension and cardiovascular disease (14, 15).

The primary hypothesis to be tested in this study was whether moderate exercise training would result in an improvement of vessel wall properties of large arteries in sedentary men. Furthermore, the possibility that improved vessel wall properties might be associated with changes in neurohumoral parameters (i.e. plasma catecholamines, ANP, and plasma renin) was investigated.

SUBJECTS AND METHODS

Subjects

Nineteen healthy male subjects entered the study. They were all non-smokers. None of the subjects had been engaged in regular sport activities for more than 1 h/week over the last 2 years and their life style and jobs were sedentary. They aged 37 years (range 22-44 y), weighed 77 kg (range 58-95 kg) and were 179 cm tall (range 169-186 cm). Casual systolic/diastolic blood pressure was up to 160/100 mmHg.

Study design

Each subject gave written informed consent. The protocol was approved by the Ethical Committee of the University of Limburg. Subjects entered a randomized, two-way, cross-over study, consisting of either continuation of their sedentary life style for 6 weeks or 6 weeks of exercise training on a cycle ergometer at a previously determined workload of 75% $\text{VO}_{2\text{max}}$ 3 times per week for 45 minutes. Physical activity, diet and weight were monitored and kept constant during the study. Compliance to the sedentary life style was promoted by weekly returns to the laboratory.

Subjects were investigated at the start of the study (data not used in analysis) and after each 6-week period. Evaluation after the training period took place 2 days after the last exercise bout. Measurements were performed

between 9 and 12 a.m. after an overnight fast and abstinence of caffeine for 12 hours, for each subject at the same time of the day.

On arrival at the laboratory, a short catheter was inserted in the v. cubitalis of the left arm, whereafter the subjects rested for at least 30 min. Hemodynamic measurements were performed in the recumbent position after another 15 min of supine rest in a quiet room ($22 \pm 1^\circ\text{C}$). The diameter (D) and relative change in diameter (distension; ΔD) during the heart cycle of the elastic right common carotid artery, the muscular right brachial artery and the muscular right common femoral artery were measured over 5 s with a vessel wall movement detector system. This system, as described by Hoeks et al (11), consists of an radio-frequency-data acquisition system, a conventional echo imager (Ultramark-V, ATL, Bothell, Washington, USA) and a personal computer. Simultaneously, blood pressure was measured with a Dinamap (Criticon, Tampa, USA). Pulse pressure (ΔP) was defined as systolic blood pressure minus diastolic blood pressure. Vessel wall properties were calculated as:

$$DC \text{ (distensibility coefficient)} = \frac{\Delta A/A}{\Delta P} = \frac{2 (\Delta D/D)}{\Delta P}$$

$$CC \text{ (cross-sectional compliance)} = \frac{\Delta V/L}{\Delta P} = \frac{\pi D * \Delta D}{2\Delta P}$$

$\Delta A/A$: relative change in cross-sectional area of the vessel

$\Delta V/L$: change in volume per unit of length

The average value of ΔD and D measured 3 times and the average value of blood pressure (BP) recorded 6 times were taken as the subject's readings. Thereafter, blood samples were obtained, with the subjects in supine position for 30 min, for determination of plasma catecholamines, plasma renin (REN) and plasma atrial natriuretic peptide (ANP) concentrations.

Blood samples were collected in 5 ml polystyrene tubes for ANP and REN and in 10 ml polystyrene chilled tubes for norepinephrine (NE) and epinephrine (E), kept on ice-water. Tubes for ANP and REN contained EDTA (1 mg). Those for NE and E were heparinized and contained 12 mg glutathione. For ANP, the peptidase inhibitor aprotinin (10,000 U/l) was added. After collection, the samples were centrifuged immediately at 4°C during 30 min at 1,500 g for NE/E and during 15 min at 1,500 g for the other hormones. Plasma was stored at -70°C until assayed.

NE and E levels were measured by means of HPLC with fluorescence detection, according to Van der Hoorn et al (17). The intra-assay coefficient of

variation was 4% for NE and 12.3% for E, the interassay coefficient of variation 6.9% for NE and 16% for E. The detection limit was 20 pg/ml for NE and 3 pg/ml for E. ANP was determined with an indirect RIA (INC-Star; Stillwater, USA) after extraction on SepPak C18 cartridges (Water Associates, Milford, Massachusetts, USA). The intra-assay coefficient of variation was 8.6% and the interassay coefficient of variation 11.6% (18). REN was quantitated with an indirect RIA as described by Derkx et al (19).

$\text{VO}_{2\text{max}}$ was determined in a progressive maximal exercise test, measuring oxygen consumption with a Sensor Medics Horizon metabolic measurement card. Data are presented as means $\pm$ S.E.M. and statistical analysis was performed according to the non-parametric Koch procedure for a two-way cross-over design using the Mann-Whitney U-test. $P < 0.05$ was considered statistically significant.

RESULTS

Endurance training increased $\text{VO}_{2\text{max}}$ from 3.13 ± 0.09 to 3.40 ± 0.08 l/min ($p < 0.01$). Resting heart rate declined from 60 ± 2 to 57 ± 2 bpm ($p < 0.05$). Resting BP, measured with the Dinamap, was $118 \pm 2/74 \pm 2$ mmHg before and $117 \pm 3/74 \pm 2$ mmHg after training. ΔP was unaltered (sedentary: 44 ± 2 mmHg; trained: 43 ± 2 mmHg). Differences in D, DC and CC of the three large arteries between the 2 periods were not statistically significant. Data are presented in Table 1. Training induced no significant changes in the various hormones measured at supine rest. Data are presented in Table 2.

Table 1. Diameter (D), distensibility coefficient (DC) and cross-sectional compliance (CC) of the right common carotid artery (CCA), right brachial artery (BA) and right common femoral artery (FA).

	Sedentary	Trained
D_{CCA} (mm)	6.39 ± 0.10	6.50 ± 0.11
D_{BA} (mm)	4.13 ± 0.08	4.17 ± 0.09
D_{FA} (mm)	8.34 ± 0.17	8.45 ± 0.18
DC_{CCA} (10^{-3} /kPa)	27.3 ± 1.7	27.5 ± 2.0
DC_{BA} (10^{-3} /kPa)	24.7 ± 2.7	22.9 ± 2.1
DC_{FA} (10^{-3} /kPa)	18.7 ± 1.6	19.4 ± 1.5
CC_{CCA} (mm^2 /kPa)	0.88 ± 0.06	0.91 ± 0.06
CC_{BA} (mm^2 /kPa)	0.32 ± 0.03	0.31 ± 0.03
CC_{FA} (mm^2 /kPa)	1.04 ± 0.09	1.10 ± 0.09

Mean values $\pm$ S.E.M.; no significant differences between sedentary and training periods.

Table 2. Plasma catecholamine concentration, plasma ANP and plasma renin at supine rest, during sedentary lifestyle and after training.

		Sedentary	Trained
Norepinephrine	(pg/ml)	229 ± 26	224 ± 11
Epinephrine	(pg/ml)	24 ± 7	20 ± 4
ANP	(pg/ml)	49 ± 11	55 ± 12
Renin	(μU/ml)	8.0 ± 0.7	7.6 ± 0.9

Mean values ± SEM; no significant differences between sedentary and training periods.

DISCUSSION

The present study provides no evidence for the hypothesis that 6 weeks of moderate exercise training can improve vessel wall properties in previously sedentary men, despite a clear increase in maximal exercise capacity of 9% and a significant decrease in resting heart rate following training. Changes in vessel wall properties could occur due to changes in transmural pressure, changes in the contractile state of the vascular smooth muscle, or due to structural changes of the vessel wall. Basal systemic arterial pressure was, however, unaltered.

This failure of training to lower blood pressure (BP) seems to contradict with most studies, finding a decrease in resting blood pressure (BP) in normotensive and hypertensive populations (20). As previously reported (16), 24-h blood pressure monitoring at the start of the study showed that 18 subjects could be classified as normotensive, based on recently proposed criteria (average 24-h BP: $126 \pm 4/80 \pm 3$ mmHg). One subject was probably hypertensive (mean 24-h BP: 139/91 mmHg).

A BP lowering effect following training, if any, is expected to be small; on the average a decline of 4 mmHg in both systolic and diastolic BP is found (20). On the other hand, our findings agree with some recent studies which have neither found a hypotensive effect on basal BP (21, 22) or on 24-hr BP (22). Furthermore, even in labile hypertensive subjects (23) or in established hypertensives (24), a failure of exercise training to lower BP has been reported (see for a detailed discussion chapter 2).

One could argue that the duration (6 weeks) or intensity (75% $\text{VO}_{2\text{max}}$) of the training program was inappropriate. However, even 4 weeks of moderate (60-70% W_{max}) exercise has shown to reduce BP significantly in sedentary normotensive subjects. With regard to the training intensity, however, there is growing support to favor mild to moderate exercise (50-60% $\text{VO}_{2\text{max}}$) (25).

Our subjects could have been physically too active, a possibility we cannot rule out in Western Europe where it is more common to habitually walk or cycle. Nevertheless, all our subjects had a sedentary lifestyle, their jobs were physically not demanding, and none of the subjects had been engaged in

regular sport activities for more than 1 h/week over the last 2 years. In addition, the sedentary leg of our experiment was closely supervised.

The absence of a change in vessel wall properties of large arteries in our study could be solely due to a failure to reduce blood pressure with training. This is supported by the findings of Gilders et al (26) who did not observe a reduction in blood pressure with conditioning and a change in pulse wave velocity both in normotensives and in hypertensives. In contrast, Cameron et al (27) reported an increased arterial compliance and a fall in systolic blood pressure in sedentary subjects after 4 weeks of training. In the latter study, it was stated that further modeling of the changes in arterial compliance suggested a contribution from alteration in pressure-independent factors in addition to a passive, pressure-dependent mechanism, although this was not substantiated by the limited data presented.

Intrinsic modification of vessel wall properties by training was also suggested by cross-sectional studies comparing trained athletes and sedentary individuals (9, 10) and a strong inverse linear relationship that was found between pulse wave velocity and physical working capacity in young men (8). In a recent study (10), we observed a higher cross-sectional compliance of the brachial artery and a tendency for a better compliance of the common femoral artery in cyclists when compared to sedentary controls, without significant differences in pulse pressure between the two groups. The better compliance of the brachial artery was due to a better arterial distensibility, probably by a decrease in muscle tone. A decrease in muscle tone could be the resultant of a decline in resting sympathetic nervous activity by endurance training or be mediated via changes in circulating hormones, e.g., the renin-angiotensin system or ANP. Alternatively, animal studies (28, 29) have provided some evidence for the fact that training is associated with a decrease in response to adrenergic stimulation at the level of the smooth muscle.

In the present study, however, no changes in resting plasma catecholamines, plasma renin or plasma ANP were detected following training. The absence of a reduction in supine basal norepinephrine levels is contradictory to most training studies, although no significant changes in resting norepinephrine concentrations have been noted by other authors in both normotensives (30) and patients with labile (23) or established hypertension (30, 31), following training. No reduction in plasma renin activity was found after 4 weeks of training in sedentary normotensive subjects (2) and in hypertensives (32), which is in agreement with the present study. In accordance with a cross-sectional study, which did not find a difference in resting plasma ANP between controls and distance runners (7), no change in plasma ANP at rest was found.

At present, the effect of training on vessel wall properties of large arteries has not been studied in hypertensives who are likely to have a reduced arterial compliance and distensibility and are possibly more likely to show an improvement after training. Oppliger and colleagues (33) trained hypertensive

rats and found lower vessel wall/lumen ratios of several large arteries in the trained compared to the untrained, resulting from similar wall thickness values but significantly larger lumen diameters.

In conclusion, a moderate exercise training program of 6 weeks does not lead to an improvement in vessel wall properties in previously sedentary subjects, despite a clear training effect on $\text{VO}_{2\text{max}}$ and a decrease in resting heart rate.

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CHAPTER 5.1

Variations in exercise systolic blood pressure in physically active middle-aged men with normal and elevated blood pressure

JAG Wijnen, MA van Baak, ES Tan, AMP Bovens, JGP Vrencken, and FTJ Verstappen

Departments of Occupational Health, Pharmacology, Movement Sciences, and Medical Informatics and Statistics, University of Limburg and Institute of Sports Medicine Limburg, Maastricht, The Netherlands

Int J Sports Med 9: 412-416, 1988

ABSTRACT

Considerable interindividual variation in the response of blood pressure to exercise has been found. In this study the response of systolic blood pressure during a progressive maximal bicycle ergometer test was investigated in 747 physically active male subjects over age of 40 years with normal, borderline elevated, and elevated resting blood pressure. The influence of several subject characteristics on this response was studied: 53% of variation in exercise systolic blood pressure (eSBP) could be explained by work load, pre-eSBP, and maximal working capacity (W_{max}). No difference in the slope of eSBP during the exercise test was seen between the three groups. Subjects with higher W_{max} had lower systolic blood pressure at the same work load compared with subjects with a lower W_{max} . Subjects in the elevated blood pressure group had significantly lower W_{max} , although maximal heart rate and lactate were similar. Other variables were not significantly associated with eSBP.

INTRODUCTION

Exercise stress testing usually includes measurements of blood pressure before, during, and for several minutes after exercise. Routine measurements during exercise are mainly performed to detect an inadequate blood pressure rise as can be due to aortic valve disease or left ventricular impairment. However, in the last decade it has also been indicated that the blood pressure response during exercise may be of diagnostic and prognostic value in various study populations. In subjects with coronary heart disease, maximal systolic blood pressure showed to be significantly related to the severity of coronary artery disease (12). Also, ratios of early recovery systolic pressure to peak systolic blood pressure have been found to be a sensitive tool for identification of patients with severe coronary artery disease (1). The blood pressure response during exercise testing has been used in the assessment of hypertension (8, 18, 21) or to detect persons at risk for future hypertension (5, 13, 26). A common finding in most of these studies is a considerable amount of intersubject variation in the response of blood pressure to exercise (8, 12, 23, 27). Factors independently contributing to this variation are insufficiently evaluated. In men, higher age, obesity index, and cigarette smoking have been shown to be associated with a more pronounced systolic blood pressure response to treadmill exercise. Regular exercise (judged by questionnaire) was not associated independently (4). On the other hand, cross-sectional studies actually measuring physical working capacity suggest that physical fitness is independently and inversely related to resting blood pressure (10). The risk of developing hypertension was found to be substantially increased with low levels of physical fitness (3). Recently, training studies have shown that regular exercise significantly lowered resting systolic and diastolic blood pressure and exercise systolic blood pressure in normotensive and untreated hypertensive sedentary subjects (14, 15, 22). It is not clear whether the reduction of exercise systolic blood pressure is merely related to a decrease in

resting blood pressure or is independently associated with an increase in physical fitness.

In this study the response of systolic blood pressure during a progressive maximal bicycle ergometer test was investigated in three different resting blood pressure groups to further evaluate the influence of several subject characteristics on this response, i.e., age, body height, body weight, body fat, supine resting DBP, supine resting SBP, supine resting heart rate, pre-exercise DBP, pre-exercise SBP, pre-exercise heart rate, smoking, alcohol consumption, exercise heart rate, and maximal working capacity.

METHODS

At three different centers for community health in the south of The Netherlands, 1840 male subjects over the age of 40 years and actively participating in sports at least 1 h/week volunteered to participate in an experimental sports-medical examination. At the three centers the same protocol and equipment were used by three especially trained physicians throughout the study. A detailed medical and family history was taken. Subjects were asked about their age, alcohol use, smoking habits, and about medication they were taking. Alcohol consumption was converted into g ethanol/week, the number of cigarettes was recorded. Anthropometric measurements taken included body height, body weight, and body fat (%), estimated from the sum of four skinfolds (6). Supine blood pressure was measured from the right upper arm by standard sphygmomanometry; if it was elevated, it was remeasured after at least another 5 min supine rest. The lowest value was taken. Fifth-phase diastolic pressures were used. Based on these casual blood pressure measurements, the participants were classified into a group with normal supine blood pressure (diastolic < 90 mmHg and systolic < 140 mmHg), borderline-elevated supine blood pressure ($90 \leq$ diastolic < 95 mmHg and/or $140 \leq$ systolic < 160 mmHg), or elevated supine blood pressure (diastolic $\geq$ 95 mmHg and/or systolic $\geq$ 160 mmHg), according to WHO criteria, excluding 65 subjects using cardiovascular drugs. Prior to the exercise test, a thorough physical examination was performed to judge whether the subjects could safely perform the test, supine heart rate was measured, and a 12-lead ECG in supine position made. Ten subjects were excluded (three for signs of recent infarction, four because of severe hypertension (diastolic > 120 mmHg), two were poorly regulated diabetics, one had a left bundle-branch block with heart murmur).

Exercise test

The subjects were seated upright on a Lode bicycle ergometer with the 3-lead (II, V1, V5) ECG electrodes in place. The test was performed with a pedal frequency between 60 and 80 rpm, starting 5 min at a work load of 100 W.

Thereafter, the work load was increased by 50 W every 2.5 min until a heart rate between 140 and 150 b/min was reached. Then the increment was 25 W every 2.5 min until exhaustion. Maximal work load ($W_{\max}$) was the highest work load that could be maintained for 2.5 min. If the final work load was not completed, $W_{\max}$ was calculated out of the completed time. Between the 3rd and 5th min of recovery, a blood sample was drawn from a cubital vein for measurement of plasma lactate concentration (LA 640 Roche)(9). This exercise test design was chosen because it allowed to evaluate the maximal working capacity ($W_{\max}$) in a relatively short time (approximately 15 min) and yet to make reliable blood pressure measurements. It has been shown that at higher work loads, a plateau in blood pressure is reached after 2 min (21). Systolic and diastolic blood pressures were recorded with standard sphygmomanometry at rest just before testing, sitting on the bicycle (pre-exercise blood pressure), and during the last 30 s of each work load. The point of muffling of Korotkoff sounds (phase IV) was taken as exercise diastolic blood pressure. During measurements, the arm was extended over the handle bars of the bicycle ergometer and supported by the physician. Heart rate was determined from the ECG at the end of each work load.

Statistical analysis

Data records of 1765 male subjects not using cardiovascular medication and having performed the exercise test were available. The measurement of exercise systolic blood pressure (esBP) at the final work load was judged to be unreliable and not included. To compare between the three blood pressure groups with respect to the means of baseline characteristics, analysis of variance (ANOVA) and two sample t-tests were performed. Differences between frequencies were evaluated by the chi square test. Significance tests were performed at the 0.05 and 0.01 levels. Inspection of individual data on esBP at different work loads suggested that a linear relationship between esBP and work load would be appropriate. At higher work loads the observed lines leveled off. Hence, a multiple regression analysis was performed with esBP as the dependent variable and work load (WL) as the independent variable and 14 prognostic factors to control for intersubject variation: age, body height, body weight, body fat, supine DBP, supine SBP, supine heart rate, pre-exercise DBP, pre-exercise SBP, pre-exercise heart rate, smoking, alcohol consumption, exercise heart rate, and $W_{\max}$. Only subjects with at least two values of esBP (i.e., exercise test with two or more submaximal work loads) were included because no linear relation can be assumed with only one measurement. As a consequence, subjects included in the analysis had a $W_{\max}$ of 150 W or more ($n = 1726$). Moreover, only subjects who fulfilled strict criteria for a maximal exercise performance (i.e., maximal heart rate $\geq (220 - \text{age})$ and plasma lactate after exercise ≥ 8 mmol/l) were included so that with greatest possible certainty true $W_{\max}$ was reached. This limited analyses to

747 subjects. To test whether the relationships between eSBP and WL were different for the three blood pressure groups, two dummy variables were introduced in the multiple regression analysis. The first dummy variable BORD (value 0 or 1) identified the borderline-elevated blood pressure group, the second dummy variable ELEV (value 0 or 1) identified the elevated blood pressure group. The decision on how many prognostic factors to retain in the final form of the regression model was made by using the all-possible subset method. That subset with the largest number of prognostic factors plus WL and the two dummy variables with regression coefficients significantly different from zero was selected and considered to be the best-fitted model. The assessment of significance was done by comparing the estimated regression coefficients relative to their standard errors with the usual 0.975 percentile of the *t*-distribution. As a by-product, the coefficient of determination R^2 was assessed. R^2 represents the proportion of total variability of the dependent variable that is accounted for by the regression model. In the multiple regression analysis, the dependence of eSBP between successive work loads within individuals was ignored. This resulted in an overestimation of the standard errors of the regression coefficient estimators. For this reason the best-fitted model according to the all-subset method might be only suboptimal. However, only the relation between WL and eSBP for the three blood pressure groups was of particular interest. The other variables were considered in the analysis only to adjust for these factors. As a consequence, the regression coefficient for WL of the best-fitted model was compared with that of the regression model containing all possible prognostic factors at hand. If the two coefficients were not substantially different than for reasons of parsimony the condensed model was considered to be a more convenient summary of data.

RESULTS

Subject characteristics for the three blood pressure groups are presented in Table 1. The subjects in the highest blood pressure group were slightly older than in the other groups. Body weight did not differ across the blood pressure groups, but the subjects with borderline elevated or elevated blood pressure had a significantly higher % body fat than the normal blood pressure group. Compared with the other groups the borderline-elevated group was slightly taller. Smoking habits and alcohol consumption did not significantly differ between the groups. Supine heart rate was lower in the normal blood pressure group. $W_{\max}$ was significantly lower in the highest blood pressure group despite the fact that maximal heart rate and plasma lactate were similar in all three groups. Average eSBP for the three groups at 100, 150, 200 and 250 W are presented in Table 2. Results from the multiple regression analysis on eSBP are shown in Table 3. The variable explaining most of the variance was work load (WL) ($R^2 = 0.386$). An additional 14.2% could be explained by pre-exercise SBP (pre-eSBP) ($R^2 = 0.099$) and $W_{\max}$ ($R^2 = 0.043$); 6.6% of

Table 1. Comparison between normal, borderline-elevated, and elevated blood pressure groups.

Variables (means $\pm$ SD)	blood pressure		
	Normal (n=322)	Borderline-elevated (n=278)	Elevated (n=147)
Age (y)	46.4 $\pm$ 4.8	47.2 $\pm$ 6.4	48.4 $\pm$ 6.4 **
Body height (cm)	175.2 $\pm$ 6.2	175.5 $\pm$ 6.1 *	174.2 $\pm$ 6.3
Body weight (kg)	77.1 $\pm$ 8.0	78.1 $\pm$ 8.2	78.1 $\pm$ 7.8
Body fat (%)	22.5 $\pm$ 5.0 **	23.8 $\pm$ 4.7	24.7 $\pm$ 4.9 **
Smokers (%)	24.8	21.7	27.2
Alcohol consumers (%)	89.1	90.1	85.7
Alcohol consumption (g/w)	139 $\pm$ 112	136 $\pm$ 114	154 $\pm$ 132
Supine SBP (mmHg)	126.0 $\pm$ 7.5 **	138.9 $\pm$ 7.5 **	149.2 $\pm$ 12.0 **
Supine DBP (mmHg)	80.8 $\pm$ 4.4 **	88.0 $\pm$ 3.4 **	96.8 $\pm$ 4.5 **
Supine HR (bpm)	62.6 $\pm$ 7.8 **	64.6 $\pm$ 8.6 **	68.0 $\pm$ 9.5 **
Pre-exercise SBP (mmHg)	127.5 $\pm$ 10.4 **	134.3 $\pm$ 10.9 **	144.8 $\pm$ 12.5 **
Pre-exercise DBP (mmHg)	84.6 $\pm$ 6.1 **	89.3 $\pm$ 5.2 **	96.3 $\pm$ 5.6 **
Pre-exercise HR (bpm)	68.0 $\pm$ 10.6 **	69.7 $\pm$ 10.7 **	73.5 $\pm$ 11.1 **
W _{max} (W)	258.5 $\pm$ 43.9	258.6 $\pm$ 45.6 **	243.2 $\pm$ 46.2 **
HR _{max} (bpm)	181.9 $\pm$ 7.7	181.8 $\pm$ 10.1	181.2 $\pm$ 7.9
Plasma lactate (mmol/l)	12.0 $\pm$ 2.5	11.9 $\pm$ 2.6	11.7 $\pm$ 2.2

* $p < 0.05$; ** $p < 0.01$ (for two-sample *t*-test, based on between-group significance in ANOVA test). Asterisks after the third column refer to differences between the first and third columns. Asterisks between columns refer to differences between adjacent columns. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Table 2. Exercise systolic blood pressure (mean $\pm$ SD, mmHg) at different work loads for the normal, borderline-elevated, and elevated blood pressure groups.

Work load (W)	blood pressure		
	Normal	Borderline-elevated	Elevated
100	163 $\pm$ 15	169 $\pm$ 16	180 $\pm$ 17
n	322	278	147
150	179 $\pm$ 17	185 $\pm$ 16	197 $\pm$ 19
n	322	277	146
200	192 $\pm$ 16	198 $\pm$ 17	208 $\pm$ 18
n	291	249	115
250	201 $\pm$ 17	203 $\pm$ 16	216 $\pm$ 14
n	166	129	48

n = number of subjects

Table 3. Summary of multiple regression results on exercise systolic blood pressure.

Variable	Regression coefficient	Standard deviation	t-ratio ^a
Constant	103	3	32.27
Pre-exercise SBP	0.64	0.02	25.65
Work load	0.274	0.005	55.25
cWork load ²	-0.00059	0.00007	-8.07
cW _{max}	-0.115	0.007	-17.48
cW _{max} ²	0.00034	0.00009	3.68
BORD	1.4	0.6	2.30
ELEV	4.8	0.8	5.7

$R^2 = .594$; $s = 14.34$; R^2 = proportion variance explained by the model; s = standard deviation of the error; a = all t -ratios are significant at 0.05 level; c Work load = work load - mean work load (172.59); cW_{max} = W_{max} - mean W_{max} (264.33); BORD = dummy variable (0-1) of borderline-elevated blood pressure group; ELEV = dummy variable (0-1) of elevated blood pressure group. Regression equation is $eSBP = 92.3 + .64 \text{ pre-exercise SBP} + .474 \text{ work load} - 59 \times 10^{-5} \text{ work load}^2 - .295 W_{max} + 34 \times 10^{-5} W_{max}^2 + 1.42 \text{ BORD} + 4.83 \text{ ELEV}$

Fig. 1 Regression lines with 95% confidence bands for the relation between eSBP and work load for the normal (a), borderline-elevated (b), and elevated (c) blood pressure group.

variation was accounted for by the division of supine blood pressure in the three blood pressure groups. In addition, other prognostic variables did not independently contribute to the variation of eSBP. Fig. 1 shows regression lines with 95% confidence bands of eSBP and WL for the three blood pressure groups. Note that at high work loads the increase in eSBP becomes less. Analysis reveals it is not caused by a selection of subjects at higher work loads

Fig. 2 Regression lines of eSBP in relation to work load for three different levels of pre-exercise systolic blood pressure (110, 140, and 160 mmHg) when adjustments are made for W_{max} .

Fig. 3 Regression lines of eSBP in relation to work load for three different levels of W_{max} (200, 250, and 300 W) when adjustments are made for pre-exercise systolic blood pressure.

with a high W_{max} and low pre-eSBP. Mean increase above pre-eSBP at a work load of 100 W was 35 mmHg in the normal, borderline-elevated, and elevated blood pressure group. Figures 2 and 3 show regression lines of eSBP in relation to work load when adjustments are made for W_{max} or pre-eSBP, respectively. When W_{max} is controlled initial differences in pre-eSBP are maintained during exercise. Analysis (by introducing interaction between the dummy and other variables) showed no difference in pressure rise for dif-

ferent levels in pre-eSBP. In case pre-eSBP is controlled differences in physical working capacity are reflected. For example, a subject with a pre-eSBP of 125 mmHg and a $W_{\max}$ of 200 W has an eSBP of 168 mmHg at 100 W compared with 161 mmHg for a subject with the same pre-eSBP but a $W_{\max}$ of 250 W.

DISCUSSION

The study shows that 53% of variation in eSBP during cycle ergometry could be explained by work load, pre-eSBP and $W_{\max}$. No differences in the slope of eSBP between groups of subjects with normal, borderline-elevated, and elevated supine blood pressure were seen although absolute values were clearly different. In accordance with other studies using either treadmill testing or bicycle ergometry (4, 8, 12, 27), our study showed a wide variability of eSBP. This is reflected by the fact that work load alone explains only 39% of total variance in eSBP. Our values of eSBP during submaximal exercise are comparable with those found in a physically active population of the same age by Heck et al (11), but somewhat lower than in a study on sedentary subjects by Nordenfeldt et al (23), which could be explained by the fact that our subjects were all actively participating in sports. The main finding in our study was the negative association between eSBP and $W_{\max}$. Subjects with higher $W_{\max}$ had lower systolic blood pressures at the same work load compared to subjects with a lower $W_{\max}$. Classification of physical fitness based on a questionnaire has failed to show a relationship with eSBP (4), possibly because no reliable estimate of physical fitness was obtained. Comparison between athletes and non-athletes showed no differences in eSBP between the two groups (11), but it was not clear whether differences in resting blood pressure were considered. Training studies, on the other hand, have shown that regular moderate exercise can lower systolic blood pressure at rest and during exercise in normotensive and untreated hypertensive sedentary subjects (14, 24). Pre-training blood pressure and the magnitude of the increase in $W_{\max}$ are important determinants for the blood pressure response to training (7). Although there were differences between the three blood pressure groups with regard to age, % body fat, body height, and resting heart rate, we could not find an independent association with eSBP for these variables. Subjects in the elevated blood pressure group had significantly lower $W_{\max}$ than those in the two other groups, although maximal heart rates were similar, suggesting differences in stroke volume between the groups (2, 19). No differences in eSBP were found between the three blood pressure groups. This confirms studies by other authors (4, 12, 16, 20, 21). On the other hand, one study showed an exaggerated systolic blood pressure response during exercise in a subgroup of borderline hypertensives (8). Others have pointed to the fact that an excessive rise in SBP during exercise is mainly seen in hypertensives with advanced stages of disease (25). Subjects with severe hypertension and those using antihypertensive medication were

excluded from our study (see Methods section). Although some studies show positive associations between age and eSBP (4, 17, 19), we could not confirm an independent relationship. A possible explanation is the relatively small age range (40-63 y) in our study compared to other studies. In another study with a comparable range in age, no relationship was found between changes in eSBP and age either (12). Weight and estimated % body fat were not significantly correlated with eSBP. In treadmill testing, a strong positive association was found between Quetelet index and eSBP, with the regression coefficient growing larger with increasing duration of the test (4). It is conceivable that an independent relationship between eSBP and body weight is only found during treadmill exercise, where the intensity at a certain speed depends on body weight. Smoking (yes/no) was not associated with eSBP. For treadmill testing only positive associations with eSBP at higher work loads were found (4). Association of smoking with eSBP could be masked by a selection of our population (physically active) or a small number of smokers. There was no association between eSBP and alcohol consumption (yes/no) which is in agreement with data in male subjects (4). Pre-exercise heart rate, supine heart rate, and exercise heart rate were not independently associated with eSBP. There was a higher supine heart rate in higher blood pressure groups. There was a mean increase of 5 b/min in resting heart rate from supine to sitting position, possibly also due to some anticipation to the beginning of exercise.

The variables determined in our study explained 59% of variation in eSBP. It is reasonable to assume there are some variables we did not include in our study which influence eSBP additionally (for instance, biochemical or hormonal factors). The variability of the indirect method for blood pressure measurement itself undoubtedly also contributes to the total variation of eSBP.

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CHAPTER 5.2

Exercise systolic blood pressure in middle-aged women with normal and elevated blood pressure

JAG Wijnen, ES Tan, MA van Baak, AMP Bovens, JGP Vrencken, FTJ Verstappen, and M Schim van der Loeff

Departments of Pharmacology, Medical Informatics and Statistics, Human Biology and Movement Sciences, University of Limburg and Institute of Movement Sciences, Maastricht, The Netherlands

Int J Sports Med 1995, 16, in press

ABSTRACT

Considerable interindividual variation in the response of blood pressure to exercise has been found. Factors independently contributing to this variation are insufficiently evaluated. This especially true for women and older age groups. Reference values of progressive maximal exercise testing in middle-aged, active subjects, especially in women, are scarce. In this study, the response of systolic arterial blood pressure during a progressive maximal cycle ergometer test was investigated in 871 physically active female subjects aged 40 years or older with normal, borderline elevated and elevated blood pressure. The influence of 14 different subject characteristics on this response was studied: 63% of variation in exercise systolic blood pressure (eSBP) could be explained by work load, pre-eSBP, age and exercise heart rate. No difference in eSBP with increasing work load was found between the three groups. Subjects with higher exercise heart rates had higher systolic blood pressures at the same work load compared to subjects with lower exercise heart rates. Maximal working capacity (W_{max}) was significantly lower in the elevated blood pressure group although maximal heart rate and lactate were similar. W_{max} was age-dependent. Other subject variables were not significantly associated with eSBP. Values of eSBP for reference purposes are presented.

INTRODUCTION

Nowadays, the blood pressure response during exercise testing is often used for diagnostic and prognostic purposes. In patients with coronary heart disease, maximal systolic blood pressure was shown to be significantly related to the severity of coronary artery disease (10). The blood pressure response to exercise has been used in the assessment of hypertension (7, 14) or to detect persons at risk for future hypertension (4, 21). Considerable amount of variation in blood pressure has been reported (2).

Factors independently contributing to this variation are insufficiently evaluated. This is especially true for women and older age groups. In women, systolic blood pressure (SBP) increased more during bicycle exercise in subjects aged 50 years or older than in younger subjects (15). During submaximal treadmill exercise, a positive association was found between SBP response and age in 20 to 49 year old women but not in women of 50 years or older (3). In 20 to 49 year old women, Quetelet index and alcohol consumption were all positively associated with the SBP response to treadmill exercise, but smoking and regular exercise were not (3).

In this study the response of SBP during a progressive maximal cycle ergometer test was investigated in a large, middle-aged female population. The influence of several subject characteristics (i.e. age, body weight, body height, body fat, supine resting diastolic blood pressure (DBP), supine resting SBP, supine resting heart rate (HR), pre-exercise DBP, pre-exercise SBP, pre-exercise HR, smoking, alcohol consumption, exercise heart rate and maximal

work capacity) on SBP response to maximal exercise was studied in women with normal, borderline elevated and elevated resting blood pressure.

SUBJECTS AND METHODS

At three different centers for community health in the south of the Netherlands, 1257 female subjects over the age of 40 years and actively participating in sports at least 1 h/week volunteered to participate in an experimental sports-medical examination. Most popular types of sport were calisthenics (37%), tennis (35%), jogging (22%), and swimming (20%). On the average, the study population participated 3.5 ± 2.8 h/week in sport activities in the year preceding this examination. At the three centers the same protocol and equipment were used by three specially trained physicians throughout the study. A detailed medical and family history was taken. Subjects were asked about their age, alcohol use, smoking habits, and about any medication they were taking. Alcohol consumption was converted into g ethanol/week, the number of cigarettes per day was recorded. Anthropometric measurements taken included body weight, body height, and body fat (%), estimated from the sum of four skinfolds (6). Casual supine blood pressure was measured after 10 min rest from the right upperarm by standard mercury sphygmomanometry; if it was elevated ($\geq 140/90$ mmHg), it was remeasured after at least another 5 min supine rest. The lowest values were taken. Fifth phase diastolic pressures were used. Based on these casual blood pressure measurements, the participants were classified into a group with normal supine arterial blood pressure (diastolic < 90 mmHg and systolic < 140 mmHg), borderline elevated supine arterial blood pressure ($90 \leq$ diastolic < 95 mmHg and/or $140 \leq$ systolic < 160 mmHg), or elevated supine arterial blood pressure (diastolic ≥ 95 mmHg and/or systolic ≥ 160 mmHg), excluding 85 subjects using cardiovascular drugs. Prior to the exercise test, a thorough examination was performed to judge if the subjects could safely perform the test, supine heart rate measured, and a 12-lead ECG in supine position made. Sixteen subjects were excluded (five severe anemia, six severe hypertension (diastolic pressure > 120 mmHg), one orthopedic disability, one instable angina, three poorly regulated diabetes mellitus).

Exercise test

The subjects were seated upright on a Lode cycle ergometer with the 3-lead (II, V1, V5) ECG electrodes in place. The test was performed with a pedal frequency between 60 and 80 rpm, starting 5 min at a work load of 50 W. Thereafter, with the pedal rate fixed, the work load was increased by 50 W every 2.5 min until a heart rate between 140 and 150 beats/min was reached. Then the increment was 25 W every 2.5 min until exhaustion. Maximal work load ($W_{\max}$) was the highest work load that could be maintained for 2.5 min. If the final increment of power output could not be maintained for 2.5 min,

$W_{\max}$ was calculated with a correction for the completed time of that increment (5 W per 30 s). Between the 3rd and 5th min of recovery, a blood sample was drawn from a cubital vein for measurement of plasma lactate concentration (LA640 Roche) (8). This exercise test design was chosen because it made it possible to evaluate the maximal working capacity in a relatively short time (approx. 15 min) and yet to make reliable blood pressure measurements. It has been shown that at higher work loads a plateau in blood pressure is reached after 2 min (16). Systolic and diastolic blood pressures were recorded with standard mercury sphygmomanometry at rest just before testing, sitting on the cycle ergometer (pre-exercise blood pressure) and during the last 30 s of each work load. The point of muffling of Korotkoff sounds (phase IV) was taken as exercise diastolic blood pressure. During measurements, the arm was extended over the handle bars of the bicycle ergometer and supported by the physician. Heart rate was determined from the ECG before exercise and at the end of each work load.

Statistical analysis

Data records of 1156 female subjects not using cardiovascular medication and having performed the test were available. To compare between the three blood pressure groups with respect to baseline characteristics, analyses of variance (ANOVA) and two sample t-tests were performed. Differences between frequencies were evaluated by chi square test. Significance tests were performed at the 0.05 and 0.01 levels. Inspection of individual data on exercise systolic blood pressure (eSBP) at different work loads suggested that a linear relationship between eSBP and work load was appropriate. Hence, a multiple regression analysis was performed with eSBP at the dependent variable and work load (WL) as the independent variable and with 14 prognostic factors to control for intersubject variation: age, body height, body weight, body fat, supine DBP, supine SBP, supine heart rate, pre-exercise DBP, pre-exercise SBP, pre-exercise heart rate, smoking, alcohol consumption, exercise heart rate, and $W_{\max}$. Only subjects with at least two values of eSBP (i.e. exercise test with two or more submaximal work loads) were included because no linear relation can be assumed with only one measurement. As a consequence, subjects included in the analysis had a $W_{\max}$ of 100 W or more ($n = 1149$). Moreover, only subjects who fulfilled strict criteria for a maximal exercise performance (i.e. maximal heart rate ($\geq (200 - \text{age})$) and/or plasma lactate after exercise ≥ 6 mmol/l) were included, so that with greatest possible certainty true $W_{\max}$ was reached. This limited analysis to 817 subjects. To test whether the relationships between eSBP and WL were different for the three blood pressure groups, two dummy variables were introduced in the multiple regression analysis. The first variable BORD (value 0 or 1) identified the borderline elevated blood pressure group, the second dummy variable ELEV (value 0 or 1) identified the elevated blood pressure group. The decision on

how many prognostic factors to retain in the final form of the regression model was made by using the all-possible subset method. That subset with the largest number of prognostic factors plus WL and the two dummy variables with the regression coefficients significantly different from zero was selected and considered to be the best-fitted model. The assessment of significance was done by comparing the estimated regression coefficients relative to their standard errors with the usual 0.975 percentile of the t -distribution. As a by-product the coefficient of determination R^2 was assessed. R^2 represents the proportion of total variability of the dependent variable that is accounted for by the regression model. In the multiple regression analysis, the dependence of eSBP between successive work loads within individuals was ignored. This resulted in an overestimation of the standard errors of the regression coefficient estimators. For this reason the best-fitted model according to the all-subset method might be only suboptimal. However, only the relation between WL and eSBP for the three blood pressure groups was of particular interest. The other variables were considered in the analysis only to adjust for these factors. As a consequence, the regression coefficient for WL of the best fitted model was compared with that of the regression model containing all possible prognostic factors at hand. If the two coefficients were not substantially different than for reasons of parsimony the condensed model was considered to be a more convenient summary of data.

RESULTS

In Table 1, subject characteristics for the three blood pressure groups are shown. Subjects with borderline elevated and elevated blood pressure were significantly older, had a higher total body weight, and % body fat than subjects in the normal blood pressure group (all; $p < 0.01$). Compared with the other groups, the elevated blood pressure group had a lesser height ($p < 0.01$). Smoking habits and alcohol consumption did not differ across the groups. Supine heart rate was lower in the normal blood pressure group ($p < 0.01$). Only slight differences in maximal heart rate and similar plasma lactate in all three groups were found. $W_{\max}$ was significantly higher in the normal blood pressure group ($p < 0.05$). Analysis of covariance with $W_{\max}$ as dependent and age as independent variable showed $W_{\max}$ to be age-related. Average eSBP for the three groups at 50 W, 100 W, 150 W, and 175 W are given in Table 2. Results from the multiple regression analysis on eSBP are presented in Table 3. Most of the variance was explained by the variable work load (WL) ($R^2 = 0.414$). Pre-exercise systolic blood pressure explained 9.8% of the variation. Age ($R^2 = 0.019$) and exercise heart rate (eHR) ($R^2 = 0.032$) had a relatively small, although significant influence; 6.7% of variation was accounted for by the division of supine blood pressure in the three blood pressure groups. None of the other prognostic variables did additionally contribute to the variation of eSBP.

Table 1. Comparison between normal, borderline-elevated, and elevated blood pressure groups

Variables (means ± SD)	blood pressure		
	Normal (n=497)	Borderline elevated (n=212)	Elevated (n=108)
Age (y)	45.8 ± 5.4 **	48.5 ± 7.0 *	50.3 ± 7.3 **
Body height (cm)	164.1 ± 5.8	163.7 ± 6.3	162.3 ± 5.8 **
Body weight (kg)	62.3 ± 7.0 **	64.4 ± 7.8	65.2 ± 8.2 **
Body fat (%)	32.0 ± 5.1 **	33.8 ± 3.9 *	34.9 ± 5.3 **
Smokers (%)	20.3	17.0	17.8
Alcohol consumers (%)	71.7	75.5	70.1
Alcohol consumption (g/w)	78 ± 75	86 ± 81	81 ± 80
Supine SBP (mmHg)	123.3 ± 8.4 **	141.2 ± 7.9 **	153.2 ± 13.1 **
Supine DBP (mmHg)	79.1 ± 5.4 **	86.6 ± 4.7 **	95.8 ± 6.0 **
Supine HR (b/min)	65.3 ± 8.0 **	69.1 ± 9.9	69.3 ± 10.8 **
Pre-exercise SBP (mmHg)	122.8 ± 10.2 **	135.9 ± 11.2 **	146.9 ± 16.0 **
Pre-exercise DBP (mmHg)	80.7 ± 6.7 **	87.3 ± 7.7 **	93.7 ± 8.2 **
Pre-exercise HR (b/min)	72.2 ± 10.7 **	76.0 ± 12.5	74.1 ± 11.6
W _{max} (W)	166.2 ± 27.1 *	161.3 ± 27.5	157.6 ± 25.7 **
HR _{max} (b/min)	173.2 ± 10.9 *	171.2 ± 11.2	172.1 ± 10.6
Plasma lactate (mmol/l)	8.4 ± 2.3	8.6 ± 2.7	8.9 ± 2.6

* = $P < 0.05$; ** = $P < 0.01$ (for two sample *t*-test, based on between-group significance in ANOVA test). Asterisks after the third column refer to differences between the first and third columns. Asterisks between columns refer to differences between adjacent columns. SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

Table 2. Exercise systolic blood pressure (mean ± SD, mmHg) at different work loads for the normal, borderline-elevated, and elevated blood pressure groups

Work load (W)	blood pressure		
	Normal	Borderline elevated	Elevated
50 W	145 ± 14	159 ± 15	171 ± 21
n	497	212	108
100 W	163 ± 16	177 ± 15	187 ± 16
n	497	212	108
150 W	175 ± 15	189 ± 18	200 ± 17
n	322	126	60
175 W	183 ± 16	192 ± 16	202 ± 22
n	39	12	9

n = number of subjects

Table 3. Summary of multiple regression results on exercise systolic blood pressure

Variable	Regression coefficient	Standard deviation	t-ratio ^a
Constant	17.20	3.94	4.37
Pre-exercise SBP	0.53	0.02	21.99
Work load	0.17	0.01	15.61
Exercise heart rate	0.28	0.02	14.81
Age	0.53	0.05	11.04
BORD	5.32	0.73	7.30
ELEV	8.93	1.03	8.69

$R^2 = 0.630$; $s \pm 13.34$; R^2 = proportion of variance explained by the model; s = standard deviation of the error; a = all t -ratios are significant at 0.001 level; BORD = dummy variable (0-1) of borderline elevated blood pressure group. ELEV = dummy variable (0-1) of elevated blood pressure group. Regression equation is $eSBP = 17.2 + 0.53 \text{ pre-exercise SBP} + 0.17 \text{ work load} + 0.28 \text{ exercise heart rate} + 0.53 \text{ age} + 5.32 \text{ BORD} + 8.93 \text{ ELEV}$.

Fig. 1 Regression lines of eSBP in relation to work load for three different levels of pre-exercise systolic blood pressure (110, 140, and 160 mmHg) when adjustments are made for age and exercise heart rate.

Figures 1 and 2 show regression lines of eSBP in relation to work load when adjustments are made for age and eHR or pre-eSBP and eHR, respectively. When age and eHR are controlled initial differences in pre-eSBP are maintained during exercise. Analysis (by introducing interaction between dummy and other variables) revealed no difference in pressure rise for different levels in pre-eSBP. In case pre-eSBP and eHR are controlled differences in age are reflected. For example, a subject, 40 years of age, with a pre-eSBP of 125 mmHg has an eSBP of 155 mmHg at 100 W when eHR is 120 beats/min. A

Fig. 2 Regression lines of eSBP in relation to work load for 40, 50, and 60 years old females when adjustments are made for pre-exercise systolic blood pressure and exercise heart rate.

female subject ten years older has an eSBP of 160 mmHg with the same pre-eSBP and eHR at 100 W.

DISCUSSION

We found that 63% of variation in eSBP during cycle ergometry could be explained by work load, pre-eSBP, age and exercise heart rate. The wide variability in eSBP found by others, either during treadmill exercise (3, 10) or testing on a cycle ergometer (7) was confirmed by the fact that work load itself could account for only 41.4% of the variation. Our values of eSBP at different work loads are comparable with those found by others in studies with much smaller groups (9, 17). However, in applying our reference values it should be stressed that all our female subjects were regularly physically active. No differences in eSBP behavior were found between the three blood pressure groups. Mean increase above pre-eSBP at 100 W was 40 mmHg in all groups. In a recent study (5) no differences in eSBP-rise between normotensive and borderline hypertensive young women were found, either. Some authors point to the fact that an excessive rise in SBP during exercise is mainly seen in hypertensives with advanced stages of disease (19). These subjects were, however, excluded from our study. Age was positively and significantly related to eSBP in middle-aged women, so that an increase of 10 years of age was associated with an 5 mmHg eSBP increase for the same resting systolic blood pressure. A significant correlation between age and maximal systolic blood pressure during cycle ergometry was recently observed by Michelsen et al (15), too. It was not clear however if differences in resting SBP were considered. It has been reported that the age-related increase in SBP can be

possibly attributed to a decrease in distensibility of large arteries with age (18). We found a clear and positive association of exercise heart rate with eSBP. For every 10 beats/min difference in eHR between individuals with same age and pre-eSBP a difference of 2-3 mmHg in eSBP was found. Differences between individuals in eHR at the same work load may reflect differences in physical fitness-level (1). In middle-aged men a significant negative association between $W_{\max}$ and eSBP was found (22), but no association with eHR. The fact that in our study $W_{\max}$ was not associated with eSBP, may be because only a relative small range in $W_{\max}$ was found for women in this study (100-263 W) compared to men (150-400 W) (22) or $W_{\max}$ was mainly a reflection of genetic endowment than of physical fitness. Alternatively, one could argue that maximal oxygen consumption ($VO_{2\max}$) is a better estimate of physical fitness than $W_{\max}$. In our experience, however, the feasibility of the direct measurement of $VO_{2\max}$ is poor in large scale studies because of unfamiliarity of the subjects with the proceedings. Furthermore, in cycle ergometry $VO_{2\max}$ and $W_{\max}$ are closely related (20) and the intra-individual variation of $W_{\max}$ is lower than the intra-individual variation of $VO_{2\max}$ (13). Classification of physical fitness based on a questionnaire has failed to show a relationship with eSBP (3) possibly because no reliable estimate of physical fitness was obtained. Training studies, on the other hand, have shown that regular exercise can lower systolic blood pressure at rest and during exercise in normotensive and untreated hypertensive subjects (11, 12). Body weight, body height and % body fat were not significantly correlated with eSBP. In treadmill testing, a strong positive association was found between Quetelet index and eSBP (3). It is conceivable that an independent relationship between eSBP and body weight is only found during treadmill exercise, where the physiological load at a certain speed depends on body weight. Smoking was not associated with eSBP in women, which is in keeping with results from treadmill testing (3). There was no association between eSBP and alcohol consumption. Supine heart rate and pre-exercise heart rate were higher in the elevated blood pressure groups. There was a mean increase of 5-7 beats/min in resting heart rate from supine to sitting position in women, possibly also due to some anticipation to the beginning of exercise. We were not able to explain the remaining 37% of variation in eSBP in this study. Some authors show that education and use of gonadal hormones (especially post-menopausal estrogens) can contribute to total variation in eSBP (3). We believe that the variability of the indirect method for blood pressure measurement and biological variability in eSBP itself also explains at least part of the remaining variation.

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CHAPTER 6

Beta-blockade and lipolysis during endurance exercise

JAG Wijnen, MA van Baak, C de Haan, HAJ Struijker Boudier, FS Tan, and LMAB Van Bortel

Departments of Pharmacology, Human Biology, and Medical Informatics and Statistics, University of Limburg, Maastricht, The Netherlands

Eur J Clin Pharmacol 45: 101-105, 1993

ABSTRACT

Inhibition of adipose tissue lipolysis may be involved in the impairment of endurance capacity after administration of a β -blocker. During endurance exercise, no significant decrease in plasma glycerol and free fatty acid (NEFA) concentrations after β -blockade is found. However, the levels during recovery from exhaustion are lower after β -blockade. This study was designed to investigate whether these lower levels after exercise are due to β -blockade or to the shorter time to exhaustion after β -blocker administration. In a single-blind study, 11 well-trained male subjects (age 23 ± 0.9 yr) performed a cycle ergometer test at 70% W_{max} until exhaustion, 2 hr after intake of 80 mg propranolol. One week later, the test was repeated after intake of placebo and was stopped at the time of exhaustion of the previous test. Average exercise time was 24 ± 2 min. During exercise plasma glucose was lower, whereas plasma lactate and respiratory exchange ratio were higher on propranolol (all $p < 0.05$). Glycerol and NEFA concentrations during exercise were not significantly different comparing both conditions. Despite an identical exercise time, during recovery glycerol and NEFA concentrations were lower after propranolol treatment ($p < 0.05$). In conclusion, lipolysis is inhibited during exercise after propranolol, probably causing a shift from fat to carbohydrate combustion.

INTRODUCTION

Beta-adrenoceptor antagonists are commonly used in various cardiovascular disorders such as hypertension, coronary artery disease and cardiac arrhythmias. For many patients with these disorders dynamic physical exercise is considered to be beneficial (18). Since a large number of the physically active patients are treated with β -blocking drugs, the side-effects of blockade of β_1 - and β_2 -adrenoceptors during exercise has become the scope of numerous studies. It has been shown that β -blockade interferes with hemodynamics, energy metabolism, thermoregulation and potassium homeostasis during exercise (4, 21). Maximal aerobic exercise capacity is significantly reduced in most studies in normotensive and hypertensive subjects (21). More important from a therapeutic point of view, however, is the effect of β -blockade during endurance exercise. Endurance exercise is the performance of work at a constant submaximal intensity. Both in normotensive and hypertensive subjects, reductions in exercise time ranging from 16 to 50% were found, compared to placebo (21). The negative effect is more pronounced during non-selective blockade than during β_1 -selective blockade. The exact mechanism behind this reduced endurance performance is not yet clear. It has been suggested that a reduced exercise cardiac output is responsible or possibly a reduced rate of lipolysis or changes in potassium homeostasis (21). With regard to an inhibition of adipose tissue lipolysis, plasma glycerol and non-esterified fatty acid (NEFA) reductions ranging from 0 to 50% were found (21). In one study NEFA levels at the end of a one hour run were even higher when subjects were given β -blockers than when given placebo (13). However,

the levels during recovery from exhaustive endurance exercise are consistently found to be lower during β -blockade (14, 15). This study was designed to differentiate whether these lower NEFA levels after exercise are due to β -blockade or to a shorter time to exhaustion after β -blocker administration.

SUBJECTS AND METHODS

Eleven trained healthy males volunteered in this study. All subjects were cyclists involved in a consistent cardiorespiratory training regime. They were normotensive (blood pressure < 140/90 mmHg) and used no medication. Each subject gave written informed consent. The protocol of the study was approved by the Ethical Committee of the University of Limburg. The physical characteristics are described in table 1. Each subject completed an initial progressive maximal cycle ergometer (Lode, Groningen, The Netherlands) test without medication to determine maximal aerobic power ($W_{\max}$). This test started with a work rate of 100 W for 5 minutes, which was increased by 50 W every 3 minutes until a heart rate of 160 beats/min, whereafter the increment was 25 W every 3 minutes until exhaustion. Two days later, the subjects returned to the laboratory to perform their first endurance test, followed by a second endurance test one week later. A light standardized breakfast was taken two hours before arrival in the lab. In combination with the meal, one tablet of propranolol 80 mg was taken before the first test and one placebo tablet before the second test (single blind). Systolic and diastolic blood pressure (Hawksley random-zero, Korotkoff V) and heart rate were measured after 5 minutes of quiet sitting. The first endurance test started with a 5 minutes warming-up at 100 W; thereafter, subjects cycled at 70% $W_{\max}$ until exhaustion, which was defined as the moment the subjects were no longer able to maintain a pedalling frequency above 50 revolutions per minute. The exercise time to exhaustion was recorded. The second endurance test was performed at the same intensity until the exercise time to exhaustion of the first test, so that the same amount of work was delivered. The subjects

Table 1. Characteristics of the subjects (mean $\pm$ SEM)

Age (y)	23 $\pm$ 1
Height (cm)	182 $\pm$ 3
Weight (kg)	74 $\pm$ 4
$VO_{2\max}$ (ml.min ⁻¹)	4701 $\pm$ 171
$VO_{2\max} \cdot kg^{-1}$ (ml.min ⁻¹ .kg ⁻¹)	64 $\pm$ 2
$W_{\max}$ (watt)	340 $\pm$ 12
$R_{\max}$	1.15 $\pm$ 0.02
$HR_{\max}$ (beats.min ⁻¹)	192 $\pm$ 2

$n = 11$; $VO_{2\max}$ = maximal oxygen uptake; $W_{\max}$ = maximal aerobic power; $R_{\max}$ = maximal respiratory exchange ratio; $HR_{\max}$ = maximal heart rate

were unaware of the purpose of this procedure and were told they had to cycle to exhaustion in the second test as well. After exhaustion, the subjects cycled for 10 minutes at 75 W (recovery). Blood samples were obtained from a cubital vein for determination of plasma glycerol, non-esterified fatty acids (NEFA), lactate, glucose, and potassium concentrations. To detect changes in plasma volume, hemoglobin and hematocrit were measured (6). Heart rate, systolic and diastolic blood pressures (sphygmomanometry, Korotkoff IV during exercise) were measured. All these measurements were performed at rest, every 10 minutes during exercise, just before exhaustion and 3, 6 and 10 minutes in the recovery phase, in a sitting position. At rest and during exercise oxygen consumption and respiratory exchange ratio (R) were also measured (SensorMedics Horizon metabolic measurement cart). Subjective feelings of exertion were rated with the Borg scale every 10 minutes during exercise and at exhaustion (3). Plasma lactate and glucose levels and plasma glycerol and NEFA concentrations were measured by enzymatic autoanalyzer methods, and potassium levels by flame photometry (Instrumentation Laboratory 243).

Results are presented as mean values $\pm$ SEM. Statistical analysis was performed by Zerbe's test for response curves (23). The Wilcoxon-test was used for two-point pairwise comparison. Statistical significance was established at $p < 0.05$.

RESULTS

At rest, sitting systolic blood pressure was reduced from 128 ± 5 mmHg after placebo to 115 ± 4 mmHg during beta-blockade ($p < 0.01$), while sitting diastolic pressure was unaffected (73 ± 3 mmHg and 77 ± 3 mmHg respectively). Heart rate was significantly reduced from 67 ± 3 beats.min⁻¹ on placebo to 51 ± 2 beats.min⁻¹ during beta-blockade ($p < 0.01$). Exercise time was 24 ± 2 minutes in the first endurance test (propranolol) and as a consequence of the design of the study the same in the second (placebo) test. Rating of perceived exertion at the end of exercise was significantly higher during propranolol (18.2 ± 0.3 vs. 12.5 ± 0.7 ; $p < 0.05$). Exercise systolic blood pressure was significantly lower during propranolol than during placebo treatment (figure 1). After 20 minutes of exercise blood pressure during placebo was $189 \pm 4/71 \pm 6$ mmHg and $166 \pm 3/65 \pm 5$ mmHg during propranolol ($p < 0.01$ for systolic blood pressure). Diastolic exercise blood pressure was not different. During exercise, heart rate (figure 2) was significantly reduced after propranolol (167 ± 3 vs. 124 ± 2 beats.min⁻¹; $p < 0.01$). There was no statistically significant difference in plasma NEFA concentration during exercise between placebo and propranolol (figure 3). However, during recovery a clear and strong increase in plasma NEFA concentration was seen after placebo, which differed significantly from an only modest increase after propranolol ($p < 0.05$). At 10 minutes recovery, the mean plasma NEFA concentration was 0.91 ± 0.14 mmol/l after placebo and 0.45 ± 0.08 mmol/l during propranolol treatment

Fig. 1 Systolic and diastolic blood pressure during placebo and propranolol. Means and SEM are shown. For figure 1-7: all points, $n=11$ except at 20 min exercise, $n=8$. $\circ$ Placebo SBP; $\bullet$ Propranolol SBP; $\square$ Placebo DBP; $\blacksquare$ Propranolol DBP

Fig. 2 Heart rate during placebo and propranolol. Means and SEM are shown. For figure 2-7: the last point during exercise is the value at exhaustion, which is shown at the appropriate average exercise time. $\circ$ Placebo; $\bullet$ Propranolol

($p < 0.05$). Although lower after β -blockade during exercise, plasma glycerol concentrations did not differ significantly between placebo and propranolol (figure 4). During recovery the plasma glycerol concentrations were significantly higher after placebo ($p < 0.05$). In contrast to NEFA, no clear post-exercise peak was seen and glycerol concentrations gradually declined. The plasma glucose concentration decreased during the first 20 minutes after

Fig. 3 Plasma non-esterified fatty acid (NEFA) concentration during placebo and propranolol. Means and SEM are shown. ○ Placebo; ● Propranolol

Fig. 4 Plasma glycerol concentration during placebo and propranolol. Means and SEM are shown. ○ Placebo; ● Propranolol

propranolol but not on placebo (significant difference between placebo and propranolol; $p < 0.01$; figure 5). At exhaustion the plasma glucose concentration after propranolol was 3.87 ± 0.14 mmol/l compared to 4.40 ± 0.20 mmol/l at rest ($p < 0.05$). During exercise there was a higher plasma glucose concentration after placebo ($p < 0.05$). Because the average resting value for plasma glucose also differed between propranolol and placebo (4.40 ± 0.20 vs. 4.86 ± 0.15 mmol/l, $p < 0.05$) we compared the change in plasma glucose during and after exercise from resting values in the two conditions. No

Fig. 5 Plasma glucose concentration during placebo and propranolol. Means and SEM are shown. $\circ$ Placebo; $\bullet$ Propranolol

Fig. 6 Plasma lactate concentration during placebo and propranolol. Means and SEM are shown. $\circ$ Placebo; $\bullet$ Propranolol

significant differences were found. After exhaustion, the plasma glucose levels quickly rose above pre-exercise levels. Compared to placebo, differences from the resting values were higher during recovery after propranolol ($p < 0.05$). During and after exercise plasma lactate was higher after propranolol ($p < 0.05$; figure 6). After 20 minutes of exercise, plasma lactate was 5.25 ± 0.80 mmol/l after propranolol and 3.65 ± 0.43 mmol/l after placebo ($p < 0.05$). Significant differences in plasma potassium were seen during and after exercise ($p < 0.01$; figure 7). At exhaustion, the mean plasma potassium concentra-

Fig. 7 Plasma potassium concentration during placebo and propranolol. Means and SEM are shown. $\circ$ Placebo; $\bullet$ Propranolol

tion was 5.73 ± 0.14 mmol/l after propranolol and 5.01 ± 0.10 mmol/l after placebo ($p < 0.01$). VO_2 and R rose during exercise in both conditions. R was significantly higher during exercise on propranolol. After 10 minutes exercise, R was 1.09 ± 0.03 after propranolol vs 1.04 ± 0.03 after placebo. R declined towards exhaustion in both conditions. VO_2 during exercise was not different between propranolol and placebo.

DISCUSSION

The mobilization of lipids from adipose tissue plays a key role in the regulation of the energy balance at rest and during exercise. Fat is an important oxidative fuel during sustained exercise. The rate of fatty acid oxidation may be limited by the rate of release from adipose tissue, by the transport capacity of the plasma, by transport across the cells in which fatty acid oxidation takes place, or by the oxidative capacity of the muscle. In vivo, lipolysis in adipose tissue is regulated by adrenergic mechanisms at rest and during exercise. Alpha-adrenergic inhibitory effects modulate lipolysis at rest, whereas β -adrenergic stimulatory effects modulate lipolysis during exercise (1). Furthermore, human lipolysis seems to be continuously inhibited by the action of hormones and parahormones (insulin, growth hormone, prostaglandins, adenosine, nicotinic acid) (12).

Submaximal endurance performance is seriously impaired by β -blockade (21) and one of the mechanisms might be a reduction in fat supply to working muscles which causes an increased carbohydrate utilization. (11). A reduced fat supply may be caused by an inhibited lipolysis. Several studies have tried to monitor lipolysis during exercise by plasma NEFA and glycerol concentrations. It is assumed that during exercise changes in glycerol levels are a better

indicator for lipolysis than changes in NEFA, which also reflect their consumption. These studies differ with regard to the influence of a non-selective beta-blockade on the NEFA and glycerol concentrations during exercise, ranging from no statistically significant difference in this study and others (10, 13, 15) to highly significant differences (11, 14).

Variation in study protocols could give rise to different stimuli to increase lipolysis. Release of fatty acids during prolonged submaximal exercise is dependent on several factors of which intensity of exercise, duration of exercise and physical conditioning are the most important. Adipocytes in trained men are more sensitive to sympathetic stimulation (16) and conditioned subjects rely more on fat combustion during prolonged exercise (9). In our study trained cyclists performed submaximal exercise at 70% W_{max} , which is in our experience close to their normal daily routine training intensity and is sustained for at least 45-60 minutes under normal (placebo) circumstances. On the other hand, the methodology of studying lipolysis by measurement of plasma NEFA and glycerol concentration during exercise can be erroneous and may also (in part) explain the variation of results in different studies.

Plasma NEFA concentration reflects the balance between a continuing release of NEFA from adipose tissue and uptake of NEFA by the working muscle. When endurance exercise is performed to exhaustion β -blockade blunts the post-exercise peak of NEFA (15, 21). This could indicate an inhibited lipolysis, but in these studies a decrease in NEFA concentration with β -blockade goes with a concomitant shorter time to exhaustion. It therefore can be argued that this decrease reflects an early interruption of the production of free fatty acids in the adipose tissue.

This study was designed to see whether differences due to β -blockade still exist if the amount of work was fixed. During acute β -blockade with propranolol moderate exercise was performed to exhaustion and the same amount of work was performed one week later on placebo. Consequently the design was not double-blind, but the subjects were unaware of the purpose of the study, blinded for their medication and they were told to perform to exhaustion in both conditions. A 75% decrease in post-exercise NEFA and 50% decrease in post-exercise glycerol was found on propranolol, while during exercise differences never reached statistical significance. So it seems that adipose tissue lipolysis is inhibited during exercise by β -blockade, which becomes more apparent during recovery from exercise.

The reason for a rapid increase in plasma concentration of NEFA after exercise is not clear, but it is a common finding in studies on fat metabolism (2, 7, 22). After exercise there may be a continuing high rate of production of NEFA when utilization is suddenly decreased. In this way a decreased rate of production of NEFA during β -blockade can be unmasked during early recovery. An alternative hypothesis is suggested by Hodgetts et al (8). They studied fat mobilization during exercise by sampling venous blood that drains from subcutaneous tissue of the anterior abdominal wall. From that

study there is strong evidence that free fatty acids accumulate within the adipose tissue during exercise because of a limitation of transport into the systemic plasma, whereas glycerol because of its smaller size and water solubility is able to escape into the general circulation. The last could also explain the fact that in studies on fat metabolism no pronounced post-exercise peak for plasma glycerol is found.

When lipolysis is attenuated, a lower availability of NEFA for energy production in the active skeletal muscles would cause a shift from fat to carbohydrate combustion. An increased use of carbohydrates may lead to a more rapid depletion of the limited carbohydrate stores in the body and thus to early fatigue. A shift from fat to carbohydrate combustion is in line with a higher lactate production, leading to the higher plasma lactate concentration that was found during propranolol treatment. Since during endurance exercise the rate of muscle glycogen utilization has been found to be unaffected by non-selective as well as β_1 -selective blockade (5), mainly plasma glucose will be used as source for carbohydrate combustion. A small, but insignificant drop in plasma glucose was seen after propranolol treatment in this study. It could indicate that the liver is unable to produce sufficient amounts of glucose. Theoretically, one could argue that the lower levels of NEFA after exercise are due to the fact that the consumption of NEFA was higher during exercise after β -blocker treatment. This is, however, not in keeping with the higher respiratory exchange ratio found during exercise. Cleroux et al (5) by actually measuring muscle triglyceride levels suggest that the decreased exercise capacity found by non-selective beta-blockade may at least in part be due to inhibition of triglyceride hydrolysis in slow-twitch fiber by blockade of β_2 -adrenoceptors. In the same study non-selective beta-blockade, but not β_1 -selective blockade induced a significant decrease in muscle potassium with a simultaneous rise in serum potassium during exhaustive exercise. In our study a significant increase in serum potassium during submaximal exercise on propranolol was found. The mentioned effects on potassium homeostasis may induce significant changes in muscle membrane potential resulting in impaired excitability and thus contractibility of the muscle fibers, thereby contributing to the decreased exercise capacity observed with non-selective β -blockade (19).

In conclusion, the results of the present study suggest that the reduction of plasma non-esterified fatty acid concentration during recovery from exhaustive endurance exercise during non-selective β -blockade reflects attenuation of adipose tissue lipolysis during exercise.

Acknowledgements

The authors thank Monique Fuss, Annemie Gijssen and Jet Bost for excellent technical assistance, and Els Geurts and Mia Hogenboom for secretarial assistance.

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CHAPTER 7

Effect of antihypertensive treatment with carvedilol on submaximal endurance performance in patients with essential hypertension

JAG Wijnen, MA van Baak, F Hartgens, FHM Derkx, H Kuipers, HAJ Struijker Boudier, and LMAB Van Bortel

Departments of Pharmacology, Human Biology, and Physiology, University of Limburg, Maastricht, and Department of Internal Medicine, Dijkzigt Hospital, Rotterdam, The Netherlands

Submitted for publication

ABSTRACT

In a randomized cross-over study of 16 patients with mild to moderate essential hypertension, the influence of antihypertensive treatment with carvedilol, a non-selective beta-blocker with vasodilating effect on submaximal exercise performance was studied. Resting blood pressure, and systolic blood pressure and heart rate during exercise were significantly reduced during carvedilol treatment. Submaximal endurance exercise performance was reduced by 36% ($p < 0.001$). Plasma lactate and glucose levels were not influenced during exercise, but plasma non-esterified fatty acid and glycerol concentrations were significantly reduced by carvedilol treatment. Significantly higher plasma potassium concentrations were found during exercise on carvedilol. Compared to placebo conditions, plasma catecholamines and atrial natriuretic peptide concentrations were significantly higher during exercise, whereas plasma renin was reduced (-20%) although not significantly. Our results indicate that carvedilol 25 mg once daily is an effective antihypertensive drug. The hemodynamic, metabolic, and humoral effects during exercise and the effects on endurance performance of carvedilol resemble those of non-selective beta-blockers.

INTRODUCTION

Maintenance of good quality of life is a key factor in a successful and optimal treatment strategy for patients with hypertension. When treating physically active patients with hypertension, physicians should choose an antihypertensive drug that does not interfere with exercise performance. Especially, beta-blocker therapy is often accompanied by a reduced exercise tolerance and a feeling of increased exertion during exercise (1). The impairment becomes even more marked during submaximal endurance performance, which more closely mirrors leisure time sporting activity, and is more pronounced during non-selective than during beta-1 selective blockade (2).

At present, the precise mechanism underlying this impairment is incompletely understood. The hemodynamic effects of beta-blockers may play a role, because a reduction of skeletal muscle blood flow during submaximal exercise has been observed (3, 4). Alternatively, it has been suggested that inhibition of adipose tissue lipolysis or changes in potassium homeostasis may be involved (2). Currently, beta-blockers with vasodilating activity become more widely available and may prove to be an attractive alternative to classical beta-blockers in the treatment of the physically active patient by lowering blood pressure in a more physiological way: by lowering the elevated peripheral resistance usually seen in hypertension, in addition to a minor decrease in cardiac output. Studies on the effect of these drugs on endurance performance and metabolism during exercise are, however, limited.

Carvedilol is a new antihypertensive agent with both non-selective beta-blocking and vasodilating properties. Vasodilation is mainly due to alpha-1 adrenoceptor blockade (8). Carvedilol has been shown to effectively reduce blood pressure at rest and during exercise in hypertensive patients, by lower-

ing both total peripheral resistance and cardiac output (9, 10). Alpha-1 blockers have little potential for adverse effects on exercise performance and metabolism (5, 6), while they may increase exercise blood flow (7). Therefore, reduction in exercise tolerance by non-selective beta-blockade might be attenuated by alpha-1 blocker mediated increase in exercise blood flow.

The present study investigates the effects of carvedilol on exercise tolerance, perceived exertion and metabolic parameters during submaximal exercise in physically active patients with mild to moderate hypertension. Furthermore, the effect of carvedilol on some blood pressure regulatory hormones (catecholamines, atrial natriuretic peptides and renin) during exercise is studied.

PATIENTS AND METHODS

Initially, 31 patients were recruited for this study from the outpatients' clinic of the department of Internal Medicine or by newspaper advertisement. Fourteen patients did not enter the study: 10 because of normotension after the placebo wash-out period, 3 had a systolic blood pressure > 170 mmHg at rest, and one was suspected of coronary heart disease. Seventeen patients entered the study. One patient dropped out because of poor compliance and 16 subjects, all men with a mean age of 42 ± 2 years, mean body mass 78 ± 3 kg, and mean height of 175 ± 3 cm, completed the study. All had mild to moderate hypertension (mean sitting diastolic blood pressure: 91-115 mmHg). They were physically active on a recreational level. The protocol of the study was approved by the Ethics Committee of the University of Limburg (Maastricht, The Netherlands). Each subject gave written informed consent.

Design of the study

All patients underwent an extensive, preliminary examination, consisting of a complete medical history, physical examination, laboratory analyses, chest X-ray, 12-lead resting ECG, and eye-mirroring. All hypertensive patients were in WHO stage I and none had overt cardiovascular disease, or other obvious disease. The study started with a 3-week placebo wash-out period. After 2 weeks in the wash-out period, blood pressure (BP) was measured 3 times with a Hawksley random zero meter and maximal exercise capacity ($W_{\max}$) was determined on a cycle ergometer. Three days later, the subjects returned to the laboratory and performed a submaximal endurance test at 70% of their maximal exercise capacity ($W_{\max}$) for familiarization purposes.

Subjects were then treated orally in a single-blind, randomized cross-over manner with carvedilol for 2 weeks or placebo (double-dummy method) for 3 weeks. 12.5 mg Carvedilol was given for 2 days, followed by 12 days of 25 mg carvedilol once daily.

At the end of each period, sitting (after 10 min of rest) and standing blood pressure (after 2 min) (Hawksley random zero meter) and heart rate were

measured 2 hr after the last intake of medication, followed by a submaximal endurance test.

Protocol of the submaximal endurance test

The subjects were asked to avoid intensive physical exercise for 48 h preceding the examination and not to consume alcohol, coffee or nicotine on the day of the test. Exercise tests were performed at least 2 hr after the last light meal.

After insertion of a short catheter in the v. cubitalis, the subjects rested for 20 min. Subsequently, the exercise test was started. After a warming-up period at 100 Watt on a cycle ergometer (Lode, Groningen, The Netherlands), subjects exercised at the predetermined workload of 70% $W_{\max}$ until exhaustion. The test was terminated when the subject was unable to maintain a pedalling rate > 50 revolutions per min.

Just prior to the start of the test, every 10 min during exercise, at exhaustion, and after 3, 6, and 10 min of recovery, heart rate (from the electrocardiogram) and systolic and diastolic blood pressure (mercury sphygmomanometry, Korotkoff I and IV during exercise) and blood samples were obtained. The latter for determination of hemoglobin, oxygen saturation, hematocrit, plasma glycerol, non-esterified fatty acid (NEFA), lactate, glucose, and potassium concentrations. At 30 min of exercise, blood samples were obtained for determination of plasma ANP, renin (REN), prorenin (PRO), norepinephrine (NE) and epinephrine (E). Every 10 min during exercise and at exhaustion, ratings of perceived exertion were recorded using the Borg scale (11).

Methods

Plasma glycerol, NEFA, glucose, and lactate were measured by enzymatic methods and plasma potassium levels by flame photometry (Instrumentation Laboratory 243). Venous blood hematocrit (microcentrifugation) and hemoglobin and oxygen saturation (Hemoximeter OSM2, Radiometer, Copenhagen, Denmark) were determined immediately.

Blood samples were collected in 5 ml polystyrene tubes for ANP and PRA and in 10 ml polystyrene chilled tubes for NE and E, kept on ice-water. Tubes for ANP and PRA contained EDTA (1 mg). Those for NE and E were heparinized and contained 12 mg of glutathione. For ANP, the peptidase inhibitor aprotinin (10,000 U/l) was added. After collection, the samples were centrifuged immediately at 4°C for 30 min at 1,500 g for NE/E and for 15 min at 1,500 g for the other hormones. Plasma was stored at -70°C until assayed.

ANP was determined with an indirect RIA (INC-star; Stillwater, USA) after extraction on SepPak C18 cartridges (Waters Associates, Milford, Massachusetts, USA). The intra-assay coefficient of variation was 8.6% and the inter-assay coefficient of variation 11.6% (12).

REN and PRO were quantitated with an indirect RIA as described by Derkx et al (13). REN and PRO concentrations as measured by this method have shown to be a valid estimate of the real renin and prorenin content in human plasma. NE and E levels were measured by means of HPLC with fluorescence detection, according to Van der Hoorn et al (14). The intra-assay coefficient of variation was 4% for NE and 12.3% for E, and the inter-assay coefficient of variation 6.9% for NE and 16% for E. The detection limit was 20 pg/ml for NE and 3 pg/ml for E.

Data analysis

Results are presented as mean $\pm$ S.E.M. Changes in plasma volume were calculated from hemoglobin and hematocrit (15). T-test or Mann-Whitney test (for humoral data) were performed to test for period effects or treatment-period interaction. Paired-t-test or Wilcoxon matched pairs test (for humoral data) were used to test for treatment effects. Zerbe's randomization test (16) was used to compare response curves. Post-hoc pairwise comparisons between groups were performed with Scheffe's F-test; $P < 0.05$ was regarded as statistically significant.

RESULTS

Blood pressure and heart rate

During carvedilol treatment, measurement of standing blood pressure immediately after a 10-minute sitting period did not show a drop of systolic blood pressure > 30 mmHg in any of the patients; in 5 patients a drop of diastolic blood pressure between 20 and 30 mmHg was measured.

No period effects or interactions occurred between the two cross-over periods. Sitting blood pressure was reduced from $136 \pm 3/95 \pm 3$ mmHg during placebo to $125 \pm 4/86 \pm 3$ mmHg during carvedilol treatment ($p < 0.0001$). Sitting heart rate did not differ significantly between placebo (66 ± 2 beats.min⁻¹) and carvedilol treatment (63 ± 3 beats.min⁻¹). Standing blood pressure decreased from $139 \pm 3/101 \pm 2$ mmHg to $123 \pm 4/91 \pm 3$ mmHg during carvedilol ($p < 0.0001$). Standing heart rate decreased from 72 ± 3 to 67 ± 3 beats.min⁻¹ ($p < 0.05$).

During exercise, systolic blood pressure was significantly lower during carvedilol treatment than during placebo treatment (Fig. 1). After 30 min of exercise, the average blood pressure during placebo was $207 \pm 5/96 \pm 3$ mmHg and was $191 \pm 7/99 \pm 4$ mmHg during carvedilol ($p < 0.01$ for systolic blood pressure). Exercise diastolic blood pressure was unaffected by carvedilol. Exercise heart rate was significantly lowered by carvedilol (Fig. 2). After 30 min of exercise, average heart rate was 160 ± 4 beats.min⁻¹ during placebo and 127 ± 4 beats.min⁻¹ during carvedilol ($p < 0.01$).

Fig. 1 Systolic and diastolic blood pressure during placebo and carvedilol treatment. Means and SEM are shown. For figures 1-7, the last point during exercise is the value at exhaustion, which is shown at the appropriate average exercise time. ○ Placebo; ● Carvedilol; ○ Placebo; ● Carvedilol

Fig. 2 Heart rate during placebo and carvedilol treatment. Means and SEM are shown. ○ Placebo; ● Carvedilol

Endurance time

Endurance time was 64 ± 4 min in the placebo exercise test and decreased during carvedilol treatment to 41 ± 4 min. This decrease of 36% was statistically significant ($p < 0.001$).

Fig. 3 Plasma glycerol concentration during placebo and carvedilol treatment. Means and SEM are shown. ○ Placebo; ● Carvedilol

Metabolic parameters

During the placebo treatment oxygen saturation of the forearm venous blood increased from $39 \pm 5\%$ at rest to $89 \pm 2\%$ at 30 min of exercise, and did not differ significantly from the carvedilol treatment. The changes in plasma volume were small ($< 7\%$) and did also not differ between the treatments.

The plasma glycerol concentration was not significantly different between the two treatment conditions at rest, but in contrast to placebo carvedilol lowered plasma glycerol both during and after exercise ($p < 0.001$; Fig. 3). At 30 min of exercise, the mean plasma glycerol concentration was 0.21 ± 0.02 mmol/l during placebo and 0.13 ± 0.02 mmol/l during carvedilol treatment ($p < 0.001$). The plasma NEFA concentrations were not statistically different at rest. During exercise, the plasma NEFA concentrations were reduced on carvedilol compared to placebo and this reduction was even more marked after exercise ($p < 0.001$; Fig. 4). At 30 min of exercise, the average plasma NEFA concentration was 0.50 ± 0.05 mmol/l during placebo and 0.29 ± 0.05 mmol/l during carvedilol ($p < 0.02$). At 10 min into recovery, the mean plasma NEFA concentration was 1.75 ± 0.16 mmol/l during placebo and 0.77 ± 0.13 mmol/l during carvedilol ($p < 0.001$).

Plasma glucose concentrations were not different at rest, during or after exercise between both conditions (Fig. 5).

Plasma lactate levels tended to be lower after carvedilol treatment at rest and during exercise, but the differences became only significant during recovery ($p < 0.01$; Fig. 6).

No statistically significant difference in plasma potassium concentration at rest was found between the treatment periods. During and after exercise, plasma potassium was increased during carvedilol treatment ($p < 0.001$; Fig.

Fig. 4 Plasma non-esterified fatty acid (NEFA) concentration during placebo and carvedilol treatment. Means and SEM are shown. ○ Placebo; ● Carvedilol

Fig. 5 Plasma glucose concentration during placebo and carvedilol treatment. Means and SEM are shown. ○ Placebo; ● Carvedilol

7). At 30 min of exercise, average plasma potassium concentration was 4.98 ± 0.09 mmol/l during placebo and 5.43 ± 0.09 mmol/l during carvedilol treatment ($p < 0.001$).

Hormones

Average ANP levels at 30 min of exercise were significantly increased from 212 ± 14 pg/ml during placebo to 391 ± 31 pg/ml during carvedilol treatment ($p < 0.001$). Both NE and E mean concentrations were significantly higher (p

Fig. 6 Plasma lactate concentration during placebo and carvedilol treatment. Means and SEM are shown. $\circ$ Placebo; $\bullet$ Carvedilol

Fig. 7 Plasma potassium concentration during placebo and carvedilol treatment. Means and SEM are shown. $\circ$ Placebo; $\bullet$ Carvedilol

< 0.001) at 30 min of exercise during carvedilol treatment (NE: 3235 ± 302 pg/ml; E: 631 ± 128 pg/ml) compared to placebo (NE: 1811 ± 169 pg/ml; E: 156 ± 15 pg/ml).

No statistically significant differences in plasma REN and PRO concentrations were found between the two treatments, although REN averaged 20% lower during carvedilol. At 30 min of exercise, average REN concentration was 35 ± 7 μ U/ml during placebo and 28 ± 6 μ U/ml during carvedilol treatment (n.s.). Average PRO concentrations were at 30 min of exercise 144 ± 12 μ U/ml during placebo treatment and 165 ± 17 μ U/ml during carvedilol (n.s.).

Perceived exertion

Ratings of perceived exertion during exercise were significantly higher ($p < 0.05$) during carvedilol treatment. At 30 min of exercise, the average Borg score was 13.1 ± 0.4 during placebo treatment and 14.0 ± 0.7 during carvedilol treatment ($p < 0.05$).

DISCUSSION

This study shows that 25 mg carvedilol given in a once daily dosing regime is effective in reducing blood pressure in patients with mild to moderate hypertension. The reduction of sitting and standing systolic and diastolic blood pressure (8-11%) during carvedilol treatment was comparable to other studies measuring supine blood pressure with the same dose of carvedilol (17, 18). A slight though significant reduction in standing, but not in sitting heart rate, was found which is in agreement with the afore-mentioned studies (17, 18). During exercise, the systolic blood pressure was significantly reduced during carvedilol treatment, which is also found in acute and chronic effect studies of carvedilol treatment using intra-arterial recordings of blood pressure (9, 10). In those studies, 25 mg of carvedilol reduced exercise diastolic blood pressure which contrasts with the present study in which no statistically significant change was found. This could be partly due to lack of accuracy of indirect auscultatory blood pressure measurement during exercise (19). On average exercise-induced tachycardia was decreased with 19% during carvedilol, which is comparable to that usually seen with a non-selective beta-blocker (20-25%)(2).

Carvedilol was found to reduce submaximal endurance exercise by an average of 36% in patients with essential hypertension, with an associated increased feeling of perceived exertion. This reduction is in line with the effects seen during antihypertensive treatment with non-selective beta-adrenergic blocking agents (approximately 40%) and larger when compared to beta-1 selective blockers (approximately 25%) (20). The metabolic effects of carvedilol during submaximal steady-state exercise found in this study were [1] a significant reduction of plasma glycerol and NEFA concentrations by 25-40%; [2] unchanged levels of plasma glucose and a tendency of lower lactate levels; [3] increased potassium levels by 5-10%. Administration of beta-1 selective or non-selective beta-blockers have found to reduce plasma glycerol and NEFA concentrations during exercise by approximately 30% (range 0-50%), slightly reduce plasma lactate and not to change plasma glucose in normally fed subjects (2). Increased plasma potassium concentrations (5-10%) during exercise after beta-blockade have usually been found (2). So the metabolic effects of carvedilol closely resemble those seen with classical beta-blocker therapy.

Both an inhibition of adipose tissue lipolysis or changes in potassium homeostasis have been postulated as mechanisms by which beta-blockade

impairs endurance performance (2). However, definite prove has yet not been found and the question how beta-blockers reduce endurance performance is still unanswered (20) (see for detailed discussion Chapter 1).

Several humoral parameters were measured at 30 min of exercise. It is a common finding that exercise increases plasma NE and E (21), plasma ANP (22) and PRA (21) in patients with essential hypertension. Compared to placebo treatment, catecholamines were significantly higher during exercise on carvedilol. This is in accordance with Omvik et al (23), who found higher catecholamine concentrations at a work load of 100 watt during carvedilol treatment and is similar to the changes normally seen with other beta-blockers without alpha-1 blocking activity (24, 25). Furthermore, these studies indicate that carvedilol (23) and beta-blockers in general (24, 25) potentiate the exercise-induced increase in plasma catecholamines. Possibly this is caused by a reduction in plasma clearance of catecholamines (26) as a consequence of a lower splanchnic-hepatic blood flow during exercise seen after beta-blocker administration (27). A possible effect of the alpha-1 blocking activity of carvedilol on plasma catecholamines cannot be ruled out, although it is reported by Omvik et al (23) that studies on isolated alpha-1 receptor blockade with prazosin and doxazosin have failed to show significant changes in plasma catecholamines.

Several studies have shown that beta-adrenoceptor blockade potentiates the exercise-induced release of ANP in healthy men (28, 29), while alpha-1 adrenoceptor blockade attenuates this increase in normotensive subjects and hypertensives (30, 31). It has been suggested that the exercise-induced increase in plasma ANP by beta-blockers may be due to atrial stretching following a decreased myocardial contractility and relaxation and not to alpha-1 adrenoceptor stimulation (30). Compared to placebo conditions, ANP levels were significantly higher during exercise after carvedilol which is in line with the afore-mentioned studies in healthy men. Omvik et al (23), however, observed only an enhanced exercise response of ANP following acute administration of a single dose of 25 mg carvedilol in a hypertensive population, but not after chronic treatment for 9 months, suggesting an adaptation in time. The exact physiological role of an induced release of ANP during exercise and its potentiation during beta-blockade is not known.

REN levels at 30 min of exercise were not significantly altered by carvedilol treatment compared to placebo. There was, however, a tendency for lower levels (-20%). It has been shown that the release of renin is at least partially mediated by beta-1 adrenergic receptors at rest and during exercise, whereas the beta-2 adrenergic receptors play only a minor or no role in the control of renin secretion, especially during exercise (32, 33). Although our data failed to show significant differences, lower levels would be in agreement with most studies finding a reduction in REN at rest and during exercise with beta-1 selective or non-selective beta-blockers (33-35). Whether the increase in REN during exercise is suppressed by beta-blockade remains controversial (33-35).

Lower levels of REN at rest and during exercise have also been observed with labetalol (36, 37), a non-selective beta-blocker with alpha-1 antagonistic activity, but not with the alpha-1 blocker prazosin (31). Chronic treatment with carvedilol reduced REN at rest in hypertensive subjects (38). PRO, a precursor of active renin, was not significantly different between the 2 treatments, although on average slightly higher levels after carvedilol treatment were seen (+15%). This could point to the possibility of reduction in negative feedback regulation of REN by angiotensin II, which, in turn, augments PRO from renal or extrarenal sources (39).

In conclusion, the study shows that carvedilol is an effective, antihypertensive drug in patients with mild to moderate essential hypertension. During exercise, metabolic and humoral effects of carvedilol resemble those seen with non-selective beta-blockers. It reduces endurance exercise capacity comparable to non-selective beta-blockers, which suggests that in physically active patients, it might not be a first line drug.

Acknowledgements

The authors thank Smith Kline Beecham Pharma BV for funding this research and J. Couvée for his valuable help in statistical analysis. The practical assistance of J. Mooij, F. Koene, C. de Haan, M. Fuss, A. Gijssen and J. Bost was greatly appreciated, as was the secretarial assistance of E. Geurts and M. Hogenboom.

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CHAPTER 8

General discussion

INTRODUCTION

Regular physical exercise has become an integral part of lifestyle modification programs for the general population because there is increasing agreement that it benefits health and promotes quality of life.

Epidemiological studies have provided evidence that individuals with low levels of physical activity and poor fitness are at greater risk to develop hypertension and cardiovascular disease (1, 2). This greater risk depends partly on a more unfavorable profile of established cardiovascular risk factors, such as blood pressure or serum cholesterol, found with a sedentary lifestyle, but even exists after taking these factors into consideration. Possibly the independence of physical inactivity as a risk factor is linked to direct changes at the level of the heart and/or vasculature.

In patients with hypertension, diabetes, CHD or osteoporosis, regular physical activity is more often considered as the first step in the prevention of further deterioration of the disease, as non-pharmacological treatment or as adjuvant to medication. When starting drug therapy, it is preferable to choose a drug that does not interfere with exercise performance.

Exercise testing has become an important tool to promote adherence to exercise programs, to screen participants to these programs and is widely used as a prognosticum and diagnosticum in various diseases (CARA, CHD, hypertension).

In the present thesis, seven studies related and relevant to the above-mentioned topics have been described.

ENDURANCE TRAINING AND BLOOD PRESSURE

There is strong evidence from training studies that regular isotonic exercise can lower resting casual blood pressure in sedentary untreated hypertensive

subjects. Studies meeting the highest scientific standards with regard to design have found an average reduction of 7 mmHg for systolic blood pressure and 5 mmHg for diastolic blood pressure (3). This modest reduction may be sufficient to normalize blood pressure in a large group of patients with borderline or mild hypertension and compares favorably with that of other non-pharmacological interventions (4).

However, one should bear in mind that the majority of studies has evaluated the effect of regular exercise on blood pressure only for weeks or months. Whether regular exercise will result in sustained and equally effective lowering of blood pressure over years remains to be established. It has been reported that some hypertensive patients were not able to maintain normotension with training beyond one year, despite an initial fall in blood pressure and good compliance to the exercise program (5). Adherence to exercise may be critical because it is likely that blood pressure will gradually return to pre-training levels on cessation of regular exercise. For most hypertensive patients, it is easier to comply to a low-intensity exercise program than to a more strenuous regimen. In this respect, there is growing support to assume that low-intensity training (approximately 50% $\text{VO}_{2\text{max}}$) is almost equally effective in lowering blood pressure as moderate-intensity training (approximately 70% $\text{VO}_{2\text{max}}$) (6).

Although blood pressure is lowered in many hypertensive patients by exercise training, the magnitude of the decrease is often not sufficient to normalize blood pressure whereas some patients do not respond at all (7). Future research should determine subsets of patients with hypertension who are not responsive to the blood pressure lowering effect of exercise training.

In normotensive sedentary subjects, a possible hypotensive action of regular endurance training still remains a matter of debate although in recent reviews (3, 8) a small average decline of 2 to 4 mmHg for systolic as well as for diastolic blood pressure at rest is assumed. Even such a small change in BP could produce a substantial reduction in cardiovascular risk in the general population. It has been estimated that a 2 mmHg downward shift in the entire distribution of systolic blood pressure in the general population might reduce the annual mortality from stroke by 6% and coronary heart disease by 4% (9). A lowering of diastolic blood pressure by 1 to 3 mmHg in subjects with high normal blood pressure may reduce the incidence of hypertension by as much as 20-50% (9).

The reason why some controlled studies failed to show any blood pressure lowering effect by endurance training is not clear. Some investigators suggested that in the basal state the effect of endurance training on blood pressure is very small if any, becoming more important, however, during conditions of stress (10). Furthermore, a small anticipated fall in blood pressure of 2-4 mmHg by training, representing a change of 2-5% from sedentary levels, could be difficult to detect, when viewed against the magnitude of a 40% fluctuation in blood pressure that can occur at random during the day (11).

Using ambulatory monitors, it is possible to achieve a 24-hour profile of blood pressure during normal daily stress and to detect smaller differences more easily by reducing within-subject variability due to a greater number of measurements. In addition, although not conclusive, evidence is growing that ambulatory blood pressure measurements are superior to traditional blood pressure measurements in providing a proper estimate of the real pressure load to the heart (12).

In chapter 2, the effect of a 6-week moderate-intensity endurance training program on ambulatory blood pressure in 19 sedentary male subjects with normal or slightly elevated resting casual blood pressure was described. Based on baseline 24-hour blood pressure, all but one of the 7 subjects with elevated casual blood pressure were judged to be normotensive. The latter pointing to an additional advantage of ambulatory monitoring, namely to better differentiate between true and pseudo-hypertensives. Endurance training resulted in a significant increase in $\text{VO}_{2\text{max}}$, clear cardiac adaptations and a decrease in total systemic vascular resistance. Despite these hemodynamic changes, blood pressure measured either at rest, during exercise or ambulatory during 24 hours was not affected by training.

To date, three other studies (13-15) have used the technique of ambulatory monitoring to evaluate the effect of endurance training on blood pressure in normotensive subjects. Like the present study none of these studies seem to indicate that endurance training lowers blood pressure at night. With regard to the effect of training on blood pressure during daily activities, studies are inconclusive. No effect on day-time blood pressure was found (13) in keeping with the present study, a significantly lowering of only diastolic day-time blood pressure was observed (14) and a significant reduction of both systolic and diastolic day-time blood pressure with endurance training has been reported (15).

The reason of the discrepancy in results between the studies is not clear. Blood pressure evaluation using the ambulatory technique could be biased by deviation in extent and intensity of daily activities between measurement days since the blood pressure profile during the day is mainly determined by physical activity (16). Further studies should therefore better document levels of physical activity during measurement days. The same holds for documentation of baseline levels of sedentary activity before enrollment in a training study. As suggested by Jennings et al (15), the antihypertensive effect of regular exercise could be a low threshold phenomenon and the major effect occurs when strictly sedentary subjects increase their activity level to only very moderate levels. Although in some studies, including the present study, subjects were judged to be sedentary because they had white-collar jobs and did not engage in regular sporting activities, their baseline levels of normal daily activities could have been already too high to show a blood pressure lowering effect by endurance training.

ENDURANCE TRAINING AND VESSEL WALL PROPERTIES OF LARGE ARTERIES

Large arteries have a conduit and buffering function and they transform the systolic flow jet from the heart into a more continuous flow for tissue perfusion. Vessel wall distensibility and arterial compliance are important vessel wall properties. Distensibility reflects the elasticity of the artery and is a determinant of the stress on the vessel wall. Compliance reflects the buffering capacity of large arteries and is an important determinant of the afterload on the heart. In aging subjects and in (borderline) hypertensive subjects, arteries become less elastic leading to a decrease in distensibility and compliance (17, 18). A decrease in arterial distensibility and compliance increases pulse pressure and left ventricular load and may play a role in the onset of atherosclerotic disease and cardiac hypertrophy (19, 20).

As described in chapter 1, physically inactive and unfit persons have a higher likelihood to develop future hypertension and are at higher risk of death from coronary heart disease and other cardiovascular diseases. Since these findings seem not to be due to confounding by conventional cardiovascular risk factors, other possible mechanisms should be considered. The objective of the studies described in chapter 3 and 4 was to investigate possible changes in vessel wall properties of large arteries at rest in relation to regular physical exercise.

In chapter 3, a cross-sectional comparison of vessel wall properties (distensibility and compliance) of the elastic common carotid artery and the muscular femoral and brachial arteries was described between cyclists and sedentary controls. The main findings of this study were a significantly higher cross-sectional compliance of the brachial artery and a tendency for a better compliance of the common femoral artery in cyclists compared to the sedentary controls, without significant differences in pulse pressure between the two groups.

Because the diameter of the brachial artery was not different between the sedentary and the trained group, whereas the distensibility coefficient was 23% higher in the trained the better compliance must be considered to be the resultant of a better vessel wall distensibility of this artery. With regard to the common femoral artery, the internal diameter was found to be 12% larger in cyclists. Most likely, this represents a local adaptation to facilitate the large blood flow to the quadriceps muscles during strenuous exercise and is structural in origin, comparable to the larger diameter of the radial artery observed in hammer-throwers (21). Distensibility coefficient of the femoral artery was not significantly different in cyclists, probably as a consequence of the structurally larger diameter. Since the diameter of the femoral artery was significantly larger in cyclists and vessel wall distensibility unchanged, an increased cross-sectional compliance of this artery could be expected. An obvious explanation for the absence of statistical significance in compliance could be the wide dispersion of individual data.

The observed findings, especially of the brachial artery, suggest that aerobic training can induce a decrease in muscle tone of predominantly muscular arteries. This is further supported by studies which found a higher regional compliance of the aorta in athletes compared to age-matched controls (22) and a strong positive relationship between aortic distensibility and physical working capacity in young men (23).

Therefore, we trained sedentary men for 6 weeks at a moderate intensity level (chapter 4). It was hypothesized that endurance training would result in an improvement of vessel wall properties of large arteries and that these changes could be dependent on or independent of a blood pressure lowering effect of training. Despite a clear training effect, judged by an increase in $\text{VO}_{2\text{max}}$ and a decrease in resting heart rate, vessel wall properties were unchanged. Because blood pressure in the basal state (after 45 min of rest) was not lowered by conditioning, it was concluded that no intrinsic modification of vessel wall properties occurred, which is in line with findings of Gilders et al (24), who did neither observe a reduction in blood pressure with training nor a change in pulse wave velocity both in normotensive and hypertensive subjects. Furthermore, in the present study basal levels of plasma catecholamines, plasma ANP and plasma renin were not changed following endurance training. On the other hand, in a recent study by Cameron et al (25) a fall in systolic blood pressure with concomitantly increased arterial compliance was found following training, which suggests a dependency of a better compliance on a reduction in transmural pressure. The combined results of chapter 3 and 4 could implicate that modification of vessel wall properties of large arteries with regular exercise is a long-term adaptation which takes months or even years to develop. Alternatively, it is possible that the observed differences between cyclists and sedentary subjects merely reflect genetic endowment. Further research should determine whether endurance training of longer duration (at least 6 months) can improve vessel wall properties of large arteries and should include subjects with (borderline) hypertension who are likely to have a decreased arterial compliance and distensibility (20).

VARIATIONS IN EXERCISE SYSTOLIC BLOOD PRESSURE

Exercise stress testing usually includes measurements of blood pressure before, during and for several minutes after exercise. In the last decades, it has been indicated that the blood pressure response during exercise may be of diagnostic and prognostic value in various populations (see chapter 1). A common finding in most of these studies is a considerable amount of intersubject variation in the response of blood pressure to exercise. Factors independently contributing to this variation are insufficiently evaluated and reference values for exercise blood pressure are rather scarce, especially in older and female populations. In chapter 5.1 (males) and chapter 5.2 (females),

the response of systolic blood pressure (eSBP) to a progressive maximal bicycle ergometer test was investigated in three large population samples of subjects 40 years or older with either normal, borderline elevated or elevated resting blood pressure. The influence of several variables on the blood pressure response was studied, including age, weight, blood pressure at rest, heart rate at rest and during exercise, smoking, alcohol consumption, and maximal work capacity. Reference values at different work loads were established for eSBP. In males, 53% of the variation in eSBP during cycle ergometry could be explained by work load, SBP at the start of the exercise test and maximal working capacity. In females, 63% of the variation in eSBP was explained by work load, SBP at the start of the exercise test, age, and exercise heart rate. In both males and females, no differences in the slope of eSBP between groups of subjects with normal, borderline elevated and elevated supine blood pressure were seen, although absolute values were clearly different, which confirms studies by other authors. It has been suggested that an excessive rise in SBP during exercise is mainly seen in hypertensives with advanced stages of disease (26); they were excluded in our studies. Subjects in the elevated blood pressure groups had a significantly lower maximal working capacity compared to the two other groups, although maximal heart rates were similar, *suggesting differences in stroke volume between the groups* (27).

The main finding in the male study was the negative association between eSBP and $W_{\max}$. Classification of physical fitness based on a questionnaire has failed to show a relationship with eSBP (28), possibly because no reliable estimate of physical fitness was obtained. In the female study, $W_{\max}$ was not associated with eSBP, possibly because of the relative small range in $W_{\max}$. On the other hand, eSBP was positively associated with exercise heart rate which could be an indicator of physical fitness (29).

A fairly large proportion of the variation in eSBP could not be explained, neither in males nor in females. We believe that at least part of the remaining variation could be accounted for by the variability of the indirect method of blood pressure measurement itself.

ENDURANCE EXERCISE AND BETA-BLOCKADE

Beta-adrenoceptor antagonists are commonly used in the treatment of various cardiovascular disorders, such as hypertension, coronary artery disease, and cardiac arrhythmias. For many patients with these disorders, dynamic physical exercise is thought to be beneficial. Since a large number of the physically active patients are treated with beta-blocking drugs, the side-effects of blockade of beta-1 and beta-2 adrenoceptors during exercise has become the scope of numerous studies. It has been shown that beta-blockade interferes with hemodynamics, energy metabolism, thermoregulation and potassium homeostasis during exercise. Maximal aerobic exercise capacity is significantly reduced in most studies in normotensive and hypertensive subjects (30).

More important from a therapeutic point of view, however, is the effect of beta-blockade during endurance exercise, i.e., the performance of work at a constant submaximal intensity. Both in normotensive and hypertensive subjects reductions in exercise time ranging from 11-55% were found compared to placebo (30).

The exact mechanism behind this reduced endurance performance is not yet clear. Both reduced exercise cardiac output and reduced rate of lipolysis or changes in potassium homeostasis have been held responsible. With regard to an inhibition of adipose tissue lipolysis, plasma glycerol and NEFA reductions ranging from 0 to 50% were found during exercise (31). During recovery from exhaustive endurance exercise however, consistently lower levels were found. These lower NEFA and glycerol levels could be the consequence rather than the cause of a shorter exercise time. Therefore, a study was designed (chapter 6) in which the amount of work performed was the same after acute administration of propranolol and placebo. While during exercise no significant differences were found in serum NEFA and glycerol concentrations between propranolol and placebo, a decrease of 75% in post-exercise NEFA and 50% in post-exercise glycerol on propranolol was found, compared to placebo. Although this study is supportive for the hypothesis that reduced availability of NEFA during exercise may be involved in the impairment of endurance exercise performance after beta-blocker administration, this was questioned by a recent study of our group (32). In this study, we increased the availability of NEFA during exercise by Intralipid (triglyceride) infusions, when healthy volunteers were treated with placebo, atenolol and propranolol. Endurance time was significantly reduced by 40% by propranolol compared to placebo and by 49% by propranolol plus Intralipid compared to placebo plus Intralipid. The results of this study do not support the lack of NEFA for energy consumption during exercise with beta-blockade. However, an effect of beta-blockade on NEFA membrane transport can not be ruled out.

In chapter 7 the effect of antihypertensive treatment with carvedilol on endurance performance was studied in patients with essential hypertension. Carvedilol is a non-selective beta-blocker with vasodilating activity. It was speculated that carvedilol would impair endurance performance to a lesser extent than classical beta-blockers because of its vasodilating properties. Furthermore, to date only limited data are available on the metabolic effects of vasodilating beta-blockers during exercise (20). Compared to placebo treatment, endurance time was reduced by 36% by carvedilol, a reduction comparable to that seen with non-selective beta-blockade (30). The hemodynamic and metabolic effects during exercise resembled those seen during non-selective beta-blockade (31). In line with other studies (31), both propranolol (chapter 5) and carvedilol (chapter 7) increased potassium levels significantly during exercise. Increased plasma potassium levels could induce significant changes in muscle membrane potential, resulting in impaired excitability and thus contractibility of muscle fibers (33), which could explain (in part) the

impairment of endurance performance by beta-blockade. The role of changes in potassium homeostasis in the impaired endurance performance by beta-blockade needs further research.

As described in chapter 1, thus far all antihypertensive agents studied have been found to reduce endurance performance, although the largest impairment in endurance performance is clearly found with beta-blockers and diuretic agents. From the viewpoint of the patient with uncomplicated hypertension who wants to engage in sporting activities, treatment with ACE-inhibitors or calcium antagonists is preferable. Based on current knowledge, these agents will only lead to a minor impairment in endurance performance and complaints about fatigue in relation to physical exercise have usually not been reported (34, 35). The therapeutic dilemma facing the physician however, is the absence at present of studies showing ACE-inhibitors and calcium-antagonists to reduce cardiovascular morbidity and mortality in contrast to beta-blockers and diuretics (36).

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Samenvatting

Uit epidemiologisch onderzoek blijkt dat lichamelijke inactiviteit en een gering lichamelijk prestatievermogen belangrijke en onafhankelijke risikofactoren zijn voor hart- en vaatziekten net zoals onder meer roken en een verhoogde bloeddruk. Tevens blijkt dat bij fysieke inactiviteit het risico op een hoge bloeddruk duidelijk toeneemt.

Verschillende studies hebben aangetoond dat een aantal risikofactoren voor hart- en vaatziekten, bijvoorbeeld het cholesterolgehalte of de bloeddruk gunstig kan worden beïnvloed door regelmatige lichamelijke activiteit. Meestal worden in deze studies vrijwilligers die een zittend bestaan leiden, getraind; dat wil zeggen, de konditie wordt verbeterd, maar of konditieverbetering per se een voorwaarde is voor een verbetering van risikofactoren staat momenteel ter discussie.

Van met name duurinspanning (fietsen, joggen) is overtuigend aangetoond dat het de bloeddruk in rust kan verlagen bij mensen met hypertensie, gemiddeld met ongeveer 7 mmHg voor de bovendruk (systolische bloeddruk) en met gemiddeld 5 mmHg voor de onderdruk (diastolische bloeddruk). Een voorwaarde is wel dat de inspanning van voldoende duur is (minstens 30 minuten) en voldoende zwaar (circa 50-70% van iemands maximaal prestatievermogen). De effecten van regelmatige duurinspanning op de bloeddruk bij gezonde mensen met een normale rust-bloeddruk zijn geringer, ongeveer 2-4 mmHg voor zowel de systolische als de diastolische bloeddruk. Door sommige onderzoekers wordt overigens betwijfeld of regelmatige inspanning de bloeddruk in rust kan verlagen, omdat zij dit in hun training-studies niet konden bevestigen. Een mogelijke verklaring hiervoor zou kunnen zijn dat het moeilijk is een klein verschil van 2-4 mmHg in bloeddruk aan te tonen bij de grote schommelingen in rust bloeddruk (tot $\pm 40\%$), gedurende de dag. Een andere verklaring veronderstelt dat een bloeddruk verlagend effect vooral wordt gezien onder meer stressvolle omstandigheden, zoals die gedurende het dagelijks leven of tijdens inspanning. In hoofdstuk 2 worden de resultaten beschreven van een studie waarbij ongetrainde vrijwilligers met een normale of licht verhoogde bloeddruk gedurende 6 weken werden getraind. De bloeddruk werd gemeten in rust (basaal nivo), tijdens inspanning en gedurende 24 uur tijdens het normale dagelijkse leven met behulp van een ambulante monitor. Ondanks een duidelijke verbetering in konditie en een daling van de hartfrequentie in rust en tijdens inspanning, was er geen effect van de training op de bloeddruk.

De efficiëntie van het hart- en vaatstelsel wordt verbeterd door regelmatige duurinspanning. Mortaliteit en morbiditeit ten gevolge van hypertensie toont een beter verband met de systolische bloeddruk dan met de diastolische bloeddruk, wat een pulsatiel stress-effekt suggereert. Vaatwandeigenschappen (kompliantie en distensibiliteit) van grote arteriën bepalen voor een belangrijk deel dit pulsatiel stress-effekt. Of deze vaatwandeigenschappen verbeteren door training is onbekend.

In hoofdstuk 3 vergeleken wij de vaatwandeigenschappen van drie grote arteriën (de a. carotis, de a. femoralis en de a. brachialis) van zeer goed getrainde wielrenners met die van ongetrainden van gelijke leeftijd, gewicht en lengte. Er bleek geen verschil in vaatwandeigenschappen van de a. carotis tussen de getrainden en ongetrainden. De diameter van de a. femoralis van de wielrenners was significant groter en de kompliantie beter, hoewel statistisch juist niet significant. De kompliantie van de a. brachialis van de wielrenners was significant beter door een grotere distensibiliteit (rekbaarheid) van de vaatwand. Deze bevindingen suggereren een mogelijke daling van spiertonus van de muskulaire arteriën door duurtraining.

In hoofdstuk 4 toetsten wij deze hypothese door ongetrainde vrijwilligers 6 weken te trainen. Wij veronderstelden hierbij dat de vaatwandeigenschappen een verbetering konden laten zien ten gevolge van een eventuele bloeddrukdaling of onafhankelijk hiervan door intrinsieke veranderingen. Ondanks een duidelijke verbetering van de VO_{2max} (konditieverbetering) na 6 weken training werden er geen verschillen gezien in de vaatwandeigenschappen. Een mogelijke verklaring hiervoor zou kunnen zijn dat het langer duurt, voordat door training vaatwandeigenschappen worden veranderd of dat de verschillen die wij zagen tussen wielrenners en ongetrainden, eerder een uitdrukking zijn van verschillen in genetische aanleg.

De laatste jaren staat de bloeddrukreactie tijdens gestandaardiseerd inspanningsonderzoek in de belangstelling. Een abnormaal sterke bloeddrukstijging bij mensen met een normale rust-bloeddruk zou een belangrijke voorspeller zijn voor het ontwikkelen van een latere hypertensie. Verder zou de bloeddrukstijging tijdens inspanningsonderzoek een betere differentiatie mogelijk maken tussen individuen met een echte hypertensie in rust en een verhoogde bloeddruk in rust ten gevolge van bijvoorbeeld spanning. Tegelijkertijd wordt echter gekonstateerd dat referentiewaarden voor bloeddruk tijdens belasting grotendeels ontbreken, vooral voor ouderen en vrouwen. Tevens blijkt er een aanzienlijke variatie tussen personen te bestaan in inspanningsbloeddruk. Het doel van de studies in hoofdstuk 5.1 (mannen) en hoofdstuk 5.2 (vrouwen) was een evaluatie van die factoren die een onafhankelijke bijdrage leveren aan de interindividuele variatie in systolische bloeddruk tijdens inspanning. Dit werd gedaan door 747 mannen en 871 vrouwen die 40 jaar of ouder waren, op een gestandaardiseerde manier op een fietsergometer te belasten en een groot aantal mogelijk prognostische factoren te onderzoeken (zoals: bloeddruk in rust, gewicht, vetpercentage, leeftijd, alcoholconsump-

tie, rookgewoonten, prestatievermogen). Bij de mannen blijkt 53% van de interindividuele variatie in systolische bloeddruk te verklaren uit fysiek belastingsnivo, de systolische bloeddruk vlak voor de start van de inspanningstest en het maximaal prestatievermogen. Bij vrouwen is 63% van de interindividuele variatie te verklaren uit fysiek belastingsnivo, systolische bloeddruk vlak voor de start van de inspanningstest, leeftijd en de hartfrequentie tijdens inspanning. Voor zowel mannen als vrouwen werden er geen verschillen gevonden in bloeddrukreactie tijdens inspanning tussen groepen met in rust een normale, borderline verhoogde of verhoogde bloeddruk. Mannen en vrouwen met een hoge bloeddruk hebben gemiddeld een lager prestatievermogen en hogere hartfrequentie in rust. Referentiewaarden voor systolische bloeddruk tijdens inspanning werden voor mannen en vrouwen voorgesteld.

Bij de behandeling van patiënten met een lichte tot matige hypertensie wordt allereerst getracht de bloeddruk te normaliseren met behulp van een aantal niet-medicamenteuze maatregelen: gewichtsreductie, beperking van zoutconsumptie en regelmatige lichamelijke inspanning. Bij een groot aantal van deze patiënten wordt echter geen adequate bloeddrukregulatie bereikt, zodat medicamenteuze behandeling noodzakelijk wordt. Beta-blokkers zijn hierbij medicijnen van eerste keuze, omdat hiervan overtuigend is aangetoond dat zij de lange-termijn complicaties van een te hoge bloeddruk beperken. Beta-blokkade vermindert echter het maximaal lichamelijk prestatievermogen aanzienlijk. Van grotere praktische betekenis is het feit dat het duurprestatievermogen belangrijk wordt beperkt. Het duurprestatievermogen wordt hierbij gedefinieerd als de volhoudtijd van een submaximale belasting, meestal ongeveer 70% van het maximaal prestatievermogen. Beta-blokkade vermindert deze volhoudtijd met gemiddeld 11-55% zowel bij normotensieve proefpersonen als bij patiënten met hypertensie. Het mechanisme waardoor het duurprestatievermogen wordt beperkt, is niet bekend. Een aantal mogelijke verklaringen is gesuggereerd: [1] een verminderd hartminuutvolume tijdens inspanning vermindert de bloedstroom naar de spieren, [2] de lipolysis in het vetweefsel wordt geremd, waardoor vrije vetzuren als energiebron minder beschikbaar zijn, of [3] de kaliumhomeostasis verandert, waardoor de prikkelbaarheid en dus het kontraktievermogen van de spiervezels afneemt. Met betrekking tot de geremde lipolysis van het vetweefsel werden er tijdens duurtesten met beta-blokkers zowel lagere, onveranderde en zelfs hogere plasma glycerol- en vrije vetzuurspiegels gevonden. Een consistente bevinding was echter dat in de herstelfase na een uitputtende duurinspanning lagere plasma glycerol- en vrije vetzuurspiegels werden gezien. Deze laatste bevinding kan echter het gevolg in plaats van de oorzaak zijn van een beperkte duurprestatie. In hoofdstuk 6 werd getracht oorzaak en gevolg te scheiden door gezonde vrijwilligers zowel tijdens beta-blokkade als tijdens placebocondities een gelijke duurprestatie te laten verrichten. Tijdens duurinspanning waren er geen significante verschillen in plasma glycerol- en vrije

vetzuurconcentraties tussen beide kondities. In de herstelfase echter waren de vrije vetzuurconcentraties 75% en de glycerolkoncentraties 50% lager tijdens beta-blokkade. Deze studie bevestigt de hypothese dat beta-blokkade de lipolysis in het vetweefsel tijdens inspanning remt.

In hoofdstuk 7 werd het effect van een nieuwe niet-selektieve beta-blokker met vaatverwijdende eigenschappen (carvedilol) op het duurprestatievermogen en metabolisme tijdens inspanning onderzocht in patiënten met essentiële hypertensie. Wij veronderstelden dat carvedilol, omdat het de bloeddruk op een meer fysiologische manier verlaagt (door een verlaging van de perifere weerstand), het prestatievermogen minder zou beperken. Uit de resultaten van deze studie blijkt echter dat carvedilol tijdens inspanning dezelfde metabole effecten laat zien als een niet-selektieve beta-blokker en dat het duurprestatievermogen met 39% wordt beperkt, vergelijkbaar met niet-selektieve beta-blokkers zonder vaatverwijdende eigenschappen.

Zoals beschreven in hoofdstuk 1, verminderen alle bloeddrukverlagende medicijnen, die tot nu toe zijn onderzocht, in meer of mindere mate het duurprestatievermogen. De grootste vermindering in duurprestatievermogen wordt echter gezien bij behandeling met beta-blokkers en diuretica. Vanuit het perspectief van de hypertensiepatiënt die lichamelijk actief wil zijn, is behandeling met ACE-remmers of calciumantagonisten te prefereren. Deze middelen verminderen het duurprestatievermogen in geringe mate en geven meestal geen vermoeidheidsklachten tijdens lichamelijke inspanning. Het therapeutische dilemma voor de behandelend arts is echter, dat van deze antihypertensiva nog niet is aangetoond dat zij een gunstig effect hebben op kardiovaskulaire morbiditeit en mortaliteit.

List of abbreviations

ANP	atrial natriuretic peptide
BA	brachial artery
BP	blood pressure
bpm	beats per minute
BORD	borderline elevated blood pressure group
CC	cross-sectional compliance
CCA	common carotid artery
CO	cardiac output
CHD	coronary heart disease
CVD	cardiovascular disease
D	diameter
ΔD	change in diameter
DBP	diastolic blood pressure
DC	distensibility coefficient
E	epinephrine
ECG	electrocardiogram
eHR	exercise heart rate
ELEV	elevated blood pressure group
eSBP	exercise systolic blood pressure
FA	femoral artery
FFA	free fatty acids
HDL	high-density lipoprotein
HR	heart rate
LDL	low-density lipoprotein
LV	left ventricle
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVMi	left ventricular mass index
NE	norepinephrine
NEFA	non-esterified fatty acids
ΔP	pulse pressure
PRA	plasma renin activity
PRO	prorenin

R	respiratory exchange ratio
R ²	coefficient of determination
RAAS	renin-angiotensin-aldosterone system
REN	renin
SBP	systolic blood pressure
SEM	standard error of the mean
SD	standard deviation
SNS	sympathetic nervous system
SV	stroke volume
SVR	systemic vascular resistance
TPR	total peripheral resistance
W	watt
WL	work load
W _{max}	maximal work capacity
VO _{2max}	maximal oxygen uptake

Dankwoord

"Vele wegen leiden naar Rome" luidt een toepasselijk gezegde. De weg naar "Rome" die ik de afgelopen drie jaar aflegde, leek soms moeilijk begaanbaar, vol hobbels, files en tal van omleggingen. Dat "Rome" toch werd bereikt, dank ik aan velen die, ieder op hun persoonlijke manier, mij steunden en stimuleerden en belangstelling bleven tonen.

Precies acht jaar heb ik gewerkt als wetenschappelijk medewerker aan een jonge, enthousiaste universiteit waaraan ik ook het genoeg had tot basisarts te mogen worden geleid.

Het was een vruchtbare periode waarin ik energieke en talentrijke collega's heb ontmoet, in het begin bij de vakgroep Arbeidsgeneeskunde en het Instituut Sportgeneeskunde Limburg (ISL) en later bij de vakgroep Farmakologie. Het ISL vormde de basis voor mijn onderzoekscarrière, waarbij Marleen van Baak vanaf het begin tot einde een waarachtig voorbeeld was. Op velerlei momenten en verschillende hoedanigheden heb ik haar leren kennen en waarderen: als leider van het ISL/DGD-project, als vertegenwoordiger van de medewerkers in het ISL-bestuur, als lid van de begeleidingskommissie bij de reorganisatie van het ISL en tenslotte als co-promotor bij mijn promotie-onderzoek, waarvoor zijn de beslissende impulsen gaf.

Frans Verstappen dank ik voor het inzetten van zijn organisatietalent, waarbij met blijvend optimisme goede voorwaarden voor onderzoek werden geboden. Fons Bovens en Sjef Vrencken, de collega-artsen van het ISL, dank ik voor hun altijd plezierige en konstruktieve samenwerking in de projecten die wij uitvoerden. Alle medewerkers van het ISL, in het bijzonder Jolanda, Marion, Gerrit, Jean, Wim en Gène, ben ik erkentelijk voor een zeer fijne samenwerking. Medewerkers van de GG en GD te Heerlen dank ik voor de jaren die ik daar gedetacheerd ben geweest, in het bijzonder mijn assistente Cécile en de heer W. Balvert.

De vakgroep Farmakologie was een tweetal jaren een hoogstaande wetenschappelijke thuisbasis voor mij. Luc Van Bortel ben ik bijzonder dankbaar voor de voortreffelijke wijze waarop hij in een korte tijd een uiterst produktieve klinisch-farmakologische sectie vormde en hieraan leiding gaf. Naast zijn uitgebreid eigen onderzoekprogramma bleek hij in staat mij altijd op een kritische manier te stimuleren tot letterlijk "good clinical practice". Hij stelde mij tevens in staat gebruik te maken van geavanceerde onderzoekstechnieken en methodieken en nam mijn financiële zorgen weg. Als co-promotor was hij immer bereid de manuskripten 's avonds te bespreken.

Mijn naaste collega Mirian Kool is een toonbeeld van ongebreidelde creativiteit en vitaliteit. Dankzij Mirian's onuitputtelijke energie en aanstekelijkheid was het mogelijk vele proefpersonen vele malen rustig en zorgvuldig te meten. Ik ben haar zeer dankbaar. Monique Fuss dank ik voor de steun, gezelligheid en goede organisatie bij mijn studies. Altijd vroeg aanwezig, stelde zij de proefpersonen op hun gemak en zorgde voor een feilloze verwerking van de talloze monsters. Claudia de Haan, begonnen als student bij de trainingsstudies, ontwikkelde zich tot een serieuze, onmisbare schakel en onderzoeker, ook bij mijn afwezigheid. Fred Hartgens was bereid een belangrijke studie af te ronden op zijn bijzondere en aimabele manier.

Jeroen Kooman haalde mij op alle fronten in met zijn onverzettelijke "drive" en vond toch altijd de rust op een boeiende wijze mijn onderzoek te ondersteunen. Jet Bost dank ik voor de zeer sekuur uitgevoerde analyses en bovendien voor de vele goede raadgevingen.

Mia Hogenboom en Els Geurts waren de reddende engelen in nood. Niet alleen hun sekretariële ondersteuning heb ik gewaardeerd, maar bovenal hun support bij het halen van de door hen vooraf gestelde deadlines.

Harry Struijker Boudier, voorzitter van de vakgroep Farmakologie en promotor, ben ik bijzonder erkentelijk voor het vertrouwen dat hij in mij stelde, het uitzicht op structuur die hij het proefschrift bood, en de vele goede adviezen die hij mij gaf bij de afronding van mijn proefschrift. Ondanks zijn drukke agenda was hij altijd tot steun.

De leden van de beoordelingskommissie dank ik voor hun kritische beoordeling. In het bijzonder Harm Kuipers, niet in de laatste plaats, omdat hij mij ook leerde hoe snel je gedachten en goede ideeën omzet in een onderzoeksvoorstel.

Bijzondere dank aan alle medewerkers van vakgroepen en diensten die mijn onderzoek mede mogelijk hebben gemaakt: Harry Wetzelaar, Frans Tan, Alex Volovics, Arnold Hoeks, Frans Smeets, Jacques Lambregts, Jaap Mooij, Fred Koene, Peter Geurten, Annemiek Gijssen, Jacques Debets en vele anderen.

Ik dank medewerkers van SmithKline Beecham BV en de Janssen Research Foundation voor hun verschillende bijdragen.

Het onderzoek zou niet mogelijk zijn geweest als de honderden proefpersonen in Limburg niet bereid waren geweest tijd, geduld en veel energie te doneren. Mijn grote dank.

Karin, jouw voortdurende steun en liefde waren onmisbaar.

Curriculum vitae

1958	Geboren 8 juni te Maastricht
1970-1976	Atheneum B, St. Maartenscollege te Maastricht
1976-1982	Studie Geneeskunde, Rijksuniversiteit Limburg, Maastricht
1981	Doctoraal examen, Rijksuniversiteit Limburg, Maastricht
1982	Artsexamen, Rijksuniversiteit Limburg, Maastricht
1983-1991	Wetenschappelijk medewerker Instituut Sportgeneeskunde Limburg
1983-1989	Wetenschappelijk medewerker vakgroep Arbeidsgeneeskunde (voorzitter: prof. dr. Tj. de Boorder), Rijksuniversiteit Limburg, Maastricht
1984-1987	Detachering bij GGD Zuid-Oost Limburg, Heerlen
1989-1991	Wetenschappelijk medewerker vakgroep Farmacologie (voorzitter: prof. dr. H.A.J. Struijker Boudier), Rijksuniversiteit Limburg, Maastricht
1991-heden	Adviserend geneeskundige, bedrijfseenheid AOV, Algemeen Burgerlijk Pensioenfonds, Heerlen en Maastricht
1992-1993	Projectcoördinator, afdeling Professionele Ondersteuning, bedrijfseenheid AOV, Algemeen Burgerlijke Pensioenfonds, Heerlen
1993-heden	Opleiding tot sociaal-geneeskundig specialist, tak verzekeringsgeneeskunde, Utrecht

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Vormgeving: Gaus van Rooij
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n: 90 5278 165 6