THE EFFECTS OF FITNESS TRAINING ON PHYSIOLOGICAL STRESS-REACTIVITY

Eco de Geus

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For the Snark *was* a Boojum, you see.

- Lewis Carroll, *The hunting of the Snark*, 1876

This thesis is mainly based on the following papers:

L.J.P. van Doornen & E.J.C. de Geus
Stress, physical activity and coronary heart disease
Work & Stress, accepted (chapter 4)

E.J.C. de Geus, L.J.P. van Doornen, A.C. de Visser & J.F. Orlebeke
Existing and training induced differences in aerobic fitness: their relationship to physiological response patterns during different types of stress
Psychophysiology 27, p457-478 1990 (chapter 5)

E.J.C. de Geus, L.J.P. van Doornen & J.F. Orlebeke
Regular exercise and aerobic fitness: influences on the psychological make-up and the physiological stress-response
Psychosomatic Medicine, under editorial revision (chapter 6)

E.J.C. de Geus, C. Kluft, A.C.W. de Bart & L.J.P. van Doornen
The effects of exercise training on plasminogen activator inhibitor activity, body fat, blood pressure and the lipid profile
Medicine Science in Sports and Exercise, in press (chapter 7)

E.J.C. de Geus & L.J.P. van Doornen
The effects of training on the physiological stress-response
Work & Stress, accepted (chapter 8.2)

Several changes were made to the original papers to avoid overlap in the contents of the introductory and discussion sections. In addition, some references to the most recent literature were included.

Contents

1. Introduction

Recent decades have witnessed an increasing popularity of leisure time sports activities in the Netherlands. From 1963 to 1988 the number of sport club members increased from 1.5 to 4.5 million[72] , and at present more than two-thirds of the adult population engages in sports activities for more than 12 times a year.[289, 368] A similar trend for increased sports behavior has been found in other industrialized countries like Germany, France, Great Britain, Japan, the United States and Canada.[290] The Canadian Fitness Survey has been a particularly important source of information on physical activity habits in the population at large.[547, 549] In this study, over 23.000 Canadians reported on their physical activity patterns in 1981 and a subsample of 4000 persons were followed for 8 years. In virtually all socio-demographic and age groups, physical activity increased from 1981 to 1988. Important motives for maintaining or taking up exercise were to feel and look better by increasing physical fitness and controlling weight, and to improve mental health, by reducing negative emotions and feelings of stress.[549, 368] These findings suggest that sports and exercise occupy an important place in the hearts and minds of an increasing number of people. Nonetheless, there remains a substantial group of people who exercise only rarely or not at all (e.g. 25% in the Netherlands[368]). Moreover, many of the people engaging in sport do so only occasionally, and a relatively small group of people exercises frequently and intensively enough to increase or maintain physical fitness.[549, 77]

Encouraged by their National Heart Associations, governments of several countries, including the Netherlands, have shown increased initiative to start instructional or promotional campaigns to encourage adoption of a more active lifestyle.[290, 29] These governmental initiatives are receiving increasing support from the corporate community. Multiple new fitness facilities have been ordered built at or near the workplace, and in the US at least 50% of the major corporations (> 750 employees) operate a corporate fitness program.[171] Popularity of fitness programs is also rapidly increasing in the Netherlands[67] and this will likely receive a further impulse from laws placing greater responsibility for the employee's health and well-being on the employer (ARBO-wet). The main goal of introducing fitness training in a work setting is to promote the employees' physical health, and, by way of that, reducing absenteeism and employee turnover and increasing work performance.[97] For the employees the attractiveness of fitness training programs is enhanced by the often quoted favorable effect on cardiovascular health. Furthermore, based on the old idea of "mens sana in corpore sano" (a healthy mind in a healthy body) fitness training is increasingly popular as a way to improve well-being and to counter work-related stress.[160] Because of the general belief that stress is bad for your heart, the idea that fitness training reduces stress further increases its attractiveness.

Outline of thesis

The popular beliefs cited above all concern complex interactions within the triangle: stress, exercise and coronary heart disease. Scientific research into these interactions has concentrated on either the beneficial effects of regular exercise, or the detrimental effects

of stress, on the development of ischaemic heart disease (IHD) and hypertension. The next two chapters of this thesis will briefly summarize the state of the art with regard to these exercise/health and stress/disease connections. Research on a third association, the direct relation between exercise and stress, has a shorter history and will be the main topic of my thesis. I will specifically focus on the assumed buffering effect of fitness training on magnitude of the bodily response to stress, because exaggerated physiological reactivity is held to be the major mechanism by which stress compromises cardiovascular health. Chapter four reviews the available cross-sectional studies on a difference in physiological stress-reactivity between regular exercisers and non-exercisers. Chapters five and six will present the results of two longitudinal studies on the effects of exercise training on psychological make-up and physiological stress-reactivity. Chapter seven will detail the effects of training on several risk factors for cardiovascular disease, including the recently found plasminogen activator inhibitor activity. These training studies were done with the support of the Dutch organization for Scientific research (NWO grant 900-564-003). In the general discussion, the available data on the interaction between stress and exercise will be reviewed, intermixed with some recommendations for future research.

2. Physical activity and cardiovascular disease

Cardiovascular disease (CVD) remains the main cause of death in the Netherlands, causing 35630 persons to die in 1988.[46] The majority of CVD deaths (67 %) is due to ischaemic heart disease (IHD), encompassing both acute myocardial infarction (AMI) and chronic cardiac ischaemia (angina pectoris). Although the number of deaths by acute myocard infarct (AMI) has slightly decreased from 1978 to 1987, the total number of patients hospitalized with ischaemic heart disease has increased. These trends seem to reflect improved treatment of ischaemic heart disease in angina and post-infarction patients, as well as a true decrease in the incidence of CVD through primary prevention.[46] Primary prevention efforts have traditionally concentrated on the behavioral modification of smoking habits and fat consumption. However, the evidence has been mounting that a sedentary life-style is also associated with increased IHD incidence, suggesting that habitual physical activity should become an important additional target for intervention. Powell et al.[459] reviewed 43 epidemiological studies on this topic. Most of them were prospective cohort studies. This type of studies follows groups with high- and low physical activity levels in time, and determines subsequent IHD incidence in these groups. Low and high activity groups were formed by selecting groups with known differences in occupational (heavy manual work versus sedentary clerks) or leisure time physical activity (regular exercisers versus sedentary), or by dividing the study population in halves/tertiles/quartiles based on self-reported activity level. A median risk ratio of 1.9 was observed across all studies, which means that heart disease occurred almost twice as often in the inactive persons as compared to the highly active.

Paying attention to the quality of studies, with respect to epidemiological methodology, accuracy of assessment of amount of physical activity, and definition of CHD endpoints, it appeared that the better studies were even more likely to report a favorable association between amount of physical activity and CHD risk. Two-thirds of the studies allowed the assessment of a dose- response relationship, e.g. by logistic regression of physical activity on disease risk. The chance of developing heart disease appeared to increase linearly with decreasing physical activity level. This finding was recently confirmed by Berlin and Colditz[26] , who applied a more quantitative approach (meta-analysis) on the data as reviewed by Powell et al.[459] , and added 8 studies that were published after Powell's review. Again a dose-response effect was observed: the difference in risk between high- and moderate active groups was smaller than between high en low active groups. They also corroborated the finding that the better studies were more likely to find a beneficial effect of physical activity. The lowest quality studies did not observe a significant association (risk ratio 1.0), whereas the studies with the highest quality observed a median risk ratio of 2.3.

Although the results reviewed point to an association between inactivity and CHD risk, this association does not necessarily represent a causal one. Theoretically, selection factors may form an alternative explanation. For instance, persons prone to develop CHD may be more likely to adopt a sedentary life style, based on their unfavorable physical constitution. Vice versa "fit" people may be more likely to apply for heavy manual work,

or to join and adhere to exercise programs. A strict proof of a causal relationship between regular physical activity and CHD would require a study that is impossible to perform: the random assignment of subjects to a life-long regimen of high- and low activity. Nevertheless, based on the well accepted criteria for causality in epidemiological research (consistency and strength of the association, dose-response relationship, biological plausibility), Powell et al.[459] concluded that the accumulated data do point to a causal relationship between physical inactivity and CHD risk.

Physical activity or fitness?

The physiological mechanisms on which the protective effect of activity is based, remain unclear. In the studies reviewed by Berlin and Colditz[26] , a few hours of regular vigorous exercise in leisure time (e.g. sports, jogging, fitness training) appeared to be as effective in lowering CHD risk as physical activities related to the occupation (e.g. farming, mail delivery, construction work), although the latter were often of longer duration. In general, the beneficial effects of regular physical activity, in any form, are thought to be mediated by increases in cardiorespiratory ("aerobic") fitness. The latter concept reflects a broad collection of physiological characteristics that distinguish the physically active from the sedentary population, and that are known to change in response to regular exercise. These effects include improvements in the vascular structure of the muscles and the heart, improved glucose tolerance and insulin sensitivity, reduced levels of blood pressure, cholesterol and triglycerides, increased fibrinolytic potential and changes in the balance of vagal-sympathetic cardiac drive, enhancing electrical stability of the heart.[49] Often, the subjects' maximal oxygen consumption during an exhaustive exercise test is used as a single index of these changes. Maximal oxygen consumption is highly predictive of endurance capacity, i.e. the ability to sustain prolonged aerobic work with large muscle groups (running, swimming, bicycling). This is particularly true when high maximal oxygen consumption is coupled to low body fat. In fact, in work physiology, maximal oxygen consumption per kg body weight (Vo_{2max}) has become synonymous with aerobic fitness.

An individual's level of aerobic fitness is only partly determined by his or her habitual physical activity habits. Twin studies have estimated that about 40 % of the interindividual variance in aerobic fitness is of genetic origin[47] (a recent study even quoted a figure as high as 71 %[158]). Therefore, a low active person may still be aerobically fit because of a favorable genetic endowment. The remaining part of the individual differences in fitness must be accounted for by current physical activity and physical activity habits earlier in life. Habitual physical activity level is difficult to measure. There are many different types of questionnaires in use, measuring physical activity over periods of a week to several years.[322] Their intercorrelation is only moderate and they have in common that they all correlate moderately with fitness as defined by maximal aerobic power. For example, in the Belgian Physical Fitness Study the correlations between activity questionnaires and the fitness level was only .10 at best![532] Other studies have found a slightly better relationship between fitness and physical activity , particularly when questionnaires on vigorous leisure time exercise were used, but the association is

far from perfect.[34, 147, 491, 207, 69] This immediately raises the question of whether physical fitness predicts longevity even better than physical activity. In the Belgian Physical Fitness Study[531] , the heart rate response to a preset physical workload (PWC150), a common index of physical fitness, was clearly related to future IHD, whereas questionnaire measures of leisure time and job activity were not. That fitness rather than activity may be the protective factor is further illustrated by the results from several recent studies where the CHD risk of the lowest fit quartile was from 4.8 to 8.5 times as high as that of the highest fit quartile.[341, 147, 35] The relative risk of 2.3 of highest active over least active tertiles, cited by Berlin & Colditz[26] , compares relatively poor to this.

The extent to which physical activity habits and/or aerobic fitness influence the CHD risk must be delineated in future studies on large populations. At present, it seems most likely that physical activity exerts its beneficial influence largely through improvements in aerobic fitness. This has consequences for the population attributable risk of physical inactivity. To achieve an improvement in aerobic fitness -up to a genetic maximum- it is necessary to exercise regularly and vigorously. The required dose of exercise will vary from individual to individual, and is known to decrease with age. As a rule of thumb, it is recommended to exercise 2 a 3 times a week with a duration of 20 minutes or more and a minimal intensity of 50 % of the maximal capacity.[621, 185] This level of activity is presently attained by a small percentage of the population only, e.g. by 8 % in the United States and 11 % in Canada.[549, 77] This leaves about 90 % of the population "at-risk" on grounds of their inactivity. In comparison, only about 10 % of the population has serum cholesterol levels above 7.0 mmol/l (which raises their CHD risk to about 2.4 times over that of persons with cholesterol levels lower than 5.5 mmol/l).[78]

Smoking and physical activity

Because of the high prevalence of a sedentary lifestyle in the population, health intervention programs targeting inactivity and fitness seem to have larger relevance than those concentrating on the traditional risk factors: smoking, cholesterol and blood pressure. However, the cardioprotective effect of physical activity and fitness may be largely caused by an inverse association with these risk factors. It seems particularly attractive to couple the strong decrease in smoking (in Dutch adult males it fell from 81 % in 1966 to 44 % in 1985) to the increasing trend in sports behavior, particularly since smoking interferes with exercise capacity. Population data on physical activity and smoking do not substantiate this idea. Smoking has been found to be unrelated to physical activity in a number of studies[187, 152, 546] , and only the more recent surveys find a weak but consistent inverse relationship between smoking and activity.[492, 549] Perhaps health practices are becoming increasingly consistent under pressure of media campaigns and improved public awareness of cardiovascular risk factors. At present however, the evidence suggests that taking up exercise per se does not cause people to quit smoking.[490, 32] The relationship of smoking with physical fitness is also inconsistent.[531, 147, 526] However, epidemiological studies assessing the fitness/smoking relationship often use

the heart rate at submaximal exercise levels as an indicator of maximal oxygen consumption. This is problematical, because smoking was seen to reduce submaximal exercise heart rate, in spite of the fact that true exercise capacity was lower in smokers.[211] Thus, the inverse relationship between fitness and smoking may be stronger than previously suggested by epidemiological studies.

Cholesterol and physical activity

The association between physical activity and CHD incidence is partly mediated by its effects on cholesterol, that is widely recognized as an important factor in atherogenesis. One's "cholesterol level" actually refers to the total cholesterol content of plasma carried on several lipoprotein families, i.e. low density lipoprotein (LDL-C), high density lipoprotein (HDL-C), and very low density lipoprotein (VLDL-C). Of these, LDL-C is generally considered to be the most atherogenic, although evidence is mounting that VLDL-C (or the highly related total triglyceride content) is also related to CHD incidence.[80] In contrast, HDL-C, assisted by lipoprotein lipase (LPL), has been shown to protect against atherosclerotic disease, most likely by removing cholesterol from the inner arterial lining.[194, 64] Apart from total cholesterol levels (TC), the ratio of LDL-C to HDL-C (or the ratio of their major peptide components apolipoprotein B and apolipoprotein A-I) is generally regarded as a good risk index for atherosclerosis. Many cross-sectional comparisons have been made between the cholesterol fractions in physically active and sedentary persons, including major epidemiological trials.[616, 492, 79] The consensus is that the physically active persons have the more favorable lipoprotein patterns, and that this is particularly pronounced for VLDL-C (triglycerides) and HDL-C, but less so for TC and LDL-C.[616] However, individual differences in various aspects of lipid metabolism appear to have a strong genetic component.[269] Therefore, a substantial part of the differences between high and low active persons may reflect constitutional differences that affect self-chosen activity level and lipid metabolism simultaneously.

Endowment for fitness may be one such factor influencing both exercise behavior and lipid metabolism, since Vo_{2max} is associated with a lower TC level[577] , a higher HDL-C level[491] and a higher Apo-A-1/Apo-B ratio.[379] Part of these associations may be due to differences in body composition. Obesity and high central to peripheral fat ratios, are the most prominent in individuals with a sedentary lifestyle[507, 549] , and the obese are least likely to take up exercise, and most likely to drop out once they have started.[312] At the same time, fat subjects are known to have an unfavorable lipid profile, that may in part be a consequence of the metabolic effects of abdominal fat itself.[31] Therefore, body composition may be an important factor influencing the relationship between exercise behavior and lipid metabolism, as well as the relationship between (weight-corrected) fitness and lipid metabolism. The association between physical activity and lipid metabolism may further be confounded with differences in the lifestyle of the physicall active and sedentaries. Reductions in dietary fat, and a shift from saturated to polysaturated fat are known to reduce plasma TC and LDL-C.[498] In contrast, a high-cholesterol diet was seen to increase LDL-C, even if subjects exercised

regularly.[278] Paradoxically, diets with low fat and high carbohydrate content also lower the level of the favorable HDL-C, even when combined with exercise.[337] Although little is known about the effects of exercising on diet, a one-year follow-up of novice runners suggested that regular exercise reduces fat intake in favor of carbohydrates.[273]

Taken the many confounding influences, the feasibility of changing the lipid metabolism by regular exercise can best be established in controlled training studies, where changes in cholesterol and its lipoprotein fractions can be directly related to exercise dose. Many of these studies have been performed, and although the results are far from consistent, the overall conclusion is that taking up exercise can reduce (V)LDL-C, and increase the HDL-C and the HDL/LDL ratio.[577, 616, 379] The effects of training on HDL-C seem to be limited to high intensity training regimes[545, 615] , and to be absent in women, who already have a high HDL-C level.[337] In spite of the consensus that the lipid profile improves with exercise, there is continuing controversy about the relative contribution of weight loss to beneficial effects of training on the lipid metabolism.[317, 572] Marti et al. showed that, in a 15 year follow-up of former elite runners, the increase in body fat was a far better predictor of the deterioration in the lipid profile than the decrease in maximal oxygen consumption or in habitual physical activity. The 8 year follow-up of the adolescent Framingham offspring showed that taking up exercise was followed by a decrease in TC, VLDL-C, and LDL-C, and an increase in HDL-C. However, only the activity-related decrease in VLDL-C remained intact when changes in the lipid profile were corrected for the changes in body mass index.[261]

From a health perspective, it clearly does not really matter to what extent the training effects on the lipid profile are mediated by weight loss or by other effects of training. The apparent conflict may be solved by regarding changes in lipid metabolism and body fat (distribution) as belonging to the same cluster, that may even include other aspects of the metabolism, like the glucose/insulin regulation.[468] Beneficial shifts in this cluster may be one of the ways in which physical activity reduces the risk for CHD.

Hypertension and physical activity

Hypertension, apart from being an important risk factor for coronary artery disease, is a serious health problem by itself. Blood pressure levels above 160/95 (15-25 % of the Dutch population) have been associated with increased risk for claudicatio intermittens, congestive heart failure and stroke.[292] However, because the disease generates little symptoms, for many people the first indication of hypertension is a fatal heart attack or stroke. Although antihypertensive medications succesfully decrease blood pressure, there are numerous side-effects associated with their use, and in mild hypertension they do not always reduce the risk for coronary heart disease. This has led to increased interest in the possible use of exercise as an alternative treatment against high blood pressure. Many studies have demonstrated an inverse association between physical activity status and blood pressure[316, 403, 437] and between high fitness levels and blood pressure[226, 33, 147] although not all studies support these findings.[490] When physical activity and fitness were both measured in the same study, only high fitness was related to low blood

pressure.[491] However, in population studies, high fitness levels are predominantly found in the young and lean. Since blood pressure is known to be higher with increasing age and body weight, the correlation of fitness with blood pressure may be spurious. Indeed, several studies correcting for weight or age, found that the correlations virtually disappeared.[515, 203, 261]

Because of the many other confounding influences that exist on the blood pressure in the population at large (salt usage, emotion, etc.), controlled training studies were again needed to directly test the possibility that blood pressure can be lowered by taking up exercise. About two-thirds of these studies (extensively reviewed in Fagard et al.[157] and Hagberg[227]) found a reduction in both DBP and SBP caused by training. Many of the studies used subjects with established hypertension and in these subjects endurance training reduced systolic and diastolic blood pressure with 10.8 and 8.2 mmHg on average.[227] This effect was generally independent of a reduction in body fat and weight. In normotensive subjects the effect of training on blood pressure is much less consistent, and on average no larger than 4 mmHg, which is about the same size as the cross-sectional difference between high and low active groups.[267] The optimal training dose needed to obtain a favorable effect is unclear at present. In the Canadian Fitness Survey, both low and high active persons had increased chance of hypertension over moderately active persons.[547] The higher blood pressure in a segment of physically active subjects may reflect the increased exercise prescription against hypertension by the physician over the past decade.[547] However, a review of training studies also suggested that blood pressure reductions are largest when training intensity is moderate only.[227] Therefore, the beneficial effects of exercise on blood pressure do not seem to require a high training intensity/frequency or a substantial increase in aerobic power.

The role of stress

In summary, the current data suggest that smoking, cholesterol and blood pressure explain part of the beneficial effect of regular exercising, although the size of the effects may not be large. To complicate matters, epidemiological data on the interrelationship of these variables among themselves do not suggest a consistent accumulation of risk factors within the same individual. For instance, smokers are less fit[532, 211] and have lower levels of HDL-C[471] , but at the same time have been found to be leaner[165] and have lower blood pressure than non-smokers.[217] More importantly, studies that have directly corrected the association between CHD and inactivity for the effects of blood pressure, cholesterol, and body mass have found the association to be only slightly reduced.[492, 126, 35] Apparently, the association between physical activity and CHD is only partly mediated by the relationship between activity and these traditional risk factors. Similarly, the association of high fitness levels and low CHD incidence is not reduced by correction for the risk factors.[147, 531, 35, 526] Two of these studies even included HDL cholesterol in their models, but still the beneficial effect of fitness was an independent one.[147, 531] Clearly, other effects of fitness (or physical activity) must be involved as well.

In search for the missing link, attention has shifted to other findings, like the improved insulin-sensitivity and glucose tolerance after training[595] , and the protection of fit subjects against sudden death and myocardial ischaemia thanks to a relative dominance of the parasympathetic nervous system over the sympathetic nervous system.[30] There is also an increasingly stronger plea for more research on the possible effects of exercise on blood coagulation.[52] Preliminary evidence suggests that disturbances in the coagulation/fibrinolytic balance may be countered by regular exercise.[611, 541] However, even the inclusion of a number of new risk indicators may still fail to explain the relationship between fitness/activity and CHD. A structural flaw in the epidemiological research on cardiovascular disease done so far, is that all studies use resting values of the risk factors in question. Thus, these studies fail to accommodate the fact that resting levels may be less relevant to later disease than average levels in daily life. The risk factors mentioned so far all deteriorate under conditions of mental load and (mild) psychosocial strain. In most work-environments such conditions are abundant. There is, for instance, a marked rise in blood pressure level and variability above resting values throughout the work-day[450, 268, 583] , that seems to be particularly pronounced among persons with borderline hypertension.[18, 570] Cholesterol too, has shown to be sensitive to psychosocial influences, particularly when these are of a severe nature, like unemployment[296] , or the threat to unemployment.[386] Thus, the incidence of CVD may be directly influenced by work-related strains. Indeed, several cross-sectional studies suggest that workers in jobs with high work demand and low job control have increased risk for hypertension and CHD (reviewed in Tyroler[586]). Using data from a 6.5 year prospective study in a cohort of 416 middle-aged blue collar men Siegrist et al.[519] showed that status inconsistency, job insecurity, work pressure and the psychological characteristic of emotional immersion ('need for control') independently predict IHD occurrence after adjusting for smoking and the resting levels of blood pressure and cholesterol. Two important points were made by this study. The first is that stressful work can directly influence health up to the point of (lethal) heart disease. Secondly, differences in the way people cope with work-related problems will serve to create differences in individual susceptibility to disease.

Clearly, failing to account for the "stress" in peoples life will limit the predictive value of known risk factors for CHD, no matter what intricate combination of factors is looked at. This may explain why, at present, the percentage of new CHD cases that can be predicted with all known risk factors combined is only about 50 %. In the same vein, the beneficial effects of physical activity may not be limited to physiological functioning at rest. In addition to that, or even specifically so, exercise may reduce the aversive consequences of stress, in particular by reducing physiological stress-reactivity.

3. Stress and cardiovascular disease

The word "stress" has become a solid part of daily Dutch vocabulary, permeating the speech of health professionals as well as the public at large. Stress is held to be largely responsible for the alarming number of people (partially) incapacitated for work or on extended sick leave, the funding of which is becoming an increasing problem to Dutch society. But what exactly is meant by stress? Three distinct uses of the term stress can be found in the literature: stress as a stimulus (as in the phrase "a stressful task"), stress as a physiological or behavioral response (e.g. "stress-reactivity") and stress as a state of disbalance, when the demands on the organism exceed its (perceived) ability to deal with these demands.[308] The latter interactionistic definition is undoubtedly the most elegant and closest to the public use of the term stress. It allows stress to incorporate radically dissimilar things like unemployment, the worried business executive, the inert body on the operating table, and the bus driver in a traffic jam. And it explains why identical problems do not cause stress to all persons, since differences in received social support, experience with the stressor and psychological make-up may affect the individual's ability to cope with problems. In fact, within the interactionistic definition, stress is simply said to occur whenever a specific combination of individual ability and situational demands give rise to the subjective experience of .. stress. This emphasis on the subjective emotional experience has led some critics to accuse health workers of using "stress" as a buzz word, that leaves little room for quantification needed for scientific research.[84] Luckily, stress can also be identified by its objective behavioral and physiological consequences.

A stressed animal can adopt a characteristic vigilant posture, attempt to flee or hide, show great restlessness or urinate or defecate more frequently than normal. It may stop feeding, exploring or interacting with its fellows. Some animals, particularly rodents, may freeze, or become motionless. When an animal has no control over its situation, or no chance of escape, it may groom, fight, or even chew on inedible substances (its cage-bars). Although extreme stressors may evoke similar behavioral responses in humans, fighting, fleeing or defecating is not the most adequate response to the bulk of stressors encountered in normal life. Behavioral signs of stress in humans are often limited to subjective report of unhappiness, job-dissatisfaction, frustration, low self-esteem, etc. When stress is prolonged it may be followed by more objective behavioral changes like alcohol, tobacco and drug usage (e.g. against insomnia), performance loss, and finally sick leave or incapacitation. Unfortunately, these objective behaviors are multicausal and probably not fit as one-to-one indicators of stress. However, both humans as well as animals respond to stress with various well-defined physiological reactions, like the release of stress-hormones in the blood (ACTH, cortisol, adrenaline, noradrenaline), sweating, and increased heart rate and blood pressure. Most of the stress research has concentrated on this readily quantifiable stress-response, particularly since repeated occurrence of this physiological stress-reactivity is held to be the crucial link between stress and disease. More often than not, the presence of the stress response has been equated with the occurrence of stress. This reliance on a response definition of stress will be echoed

throughout the present thesis.

The physiological stress response

The physiological response to stress is by no means an undifferentiated response. A major distinction is generally made between the activity of pituitary-adrenal-cortical axis and the activity of the sympathetic-adrenal-medullary system. Although most stressors evoke some combination of these responses, animal studies have shown that ACTH and cortisol release are most pronounced when the animal sees no escape and responds with depression and subordination.[239] On the other hand, situations that pose a threat to the animal but still allow active effortful coping (e.g. fight or flight) will lead to a strong increase in adrenaline release coupled to a distinct cardiovascular "defense reaction".[357, 429] This defense reaction can be reliably produced by electrical stimulation of certain areas of the brain (defense area), and causes a shift in blood distribution, such that the skeletal muscle perfusion is acutely increased at the expense of cutaneous, renal and splanchnic beds.[242] Increased cardiac β-adrenergic drive causes a rapid increase in heart rate and cardiac contractility[429, 510] , and the increased adrenaline levels in the arterial blood cause a sharp increase in calf[247] , forearm[328, 247] , and adipose tissue blood flow.[346] Apart from the effects on the cardiovascular system, stress causes increases in respiration rate, minute ventilatory volume, and irregularity of breathing, whereas abdominal breathing, tidal volume, and blood levels of CO2 are decreased.[220] These changes in respiratory pattern may play an important role in the reduction of respiratory sinus arrhythmia (RSA) seen under conditions of stress.[7, 222, 223] Since RSA corresponds tightly to vagal control over the heart[143, 458] , this phenomenon suggests that the effects of β-adrenergic activity on the heart are enhanced by withdrawal of parasympathetic influences. This stress-induced reduction of vagal cardiac control may be an important cause of the lowered carotid baroreflex sensitivity found under stress.[527, 413, 552]

Unfortunately, most studies in humans have concentrated on the heart, i.e. increases in systolic blood pressure and cardiac output, at the expense of the vascular processes, i.e. increases in diastolic blood pressure and shifts in vascular resistance. However, most stressors evoking the defense reaction give rise to substantial increases in diastolic pressure.[610, 133, 509, 254, 41] This increase in diastolic blood pressure occurs when the acute rise in cardiac output is not entirely buffered a decrease in peripheral vascular resistance. Although adrenaline causes vasodilation of the muscle-beds, there is a simultaneous increase in the vasoconstrictive activity to non-muscular tissue.[57, 58] Recent studies even demonstrated an increase in sympathetic vasoconstrictive action in the muscles themselves.[10] The result of the conflicting regional vasodilating and vasoconstrictive influences on the total peripheral resistance appears to be variable[354, 510, 5, 130] , so that different patterns of cardiovascular reactivity can be seen, even within the defense reaction. Total duration of the stressor seems to be an important determinant of the exact cardiovascular pattern found. Whereas heart rate and cardiac output show rapid habituation after stress, diastolic blood pressure remains elevated by a gradual upward shift in vascular resistance.[76, 400, 401] Even within the same task

however, there is always a subset of individuals that responds with an increase in total peripheral resistance when an increased cardiac output is the dominant response.[235, 107, 250] Concurrent measurement of cardiac output and total peripheral resistance during different types of tasks are currently used to clarify these matters.

Stress-reactivity as a CVD risk factor

Most of the physiological reactions to stress are thought to be adaptive, i.e. they are seen as a way to counter the effects of physical stress (trauma, infection, bleeding etc.) or as a physiological preparation for fight or flight in response to imminent danger. Why should this essentially adaptive mechanism predispose to disease? In the early work of Selye, emphasis was laid on exhaustion as the pathophysiological mechanism behind stress.[508] If a threat remains present during a long period of time, the prolonged state of alarm may result in exhaustion of the regulating systems ('adaptive energy'), and finally the collapse of, e.g. the immune-system facing an infectious agent. The idea that stress causes an overshoot of anti-inflammatory and immunosuppresive action is still highly prominent in research on the pituitary-adrenocortical response and psychoneuroimmunology.[200] Particularly in the field of cardiovascular psychophysiology, emphasis has shifted to uncoupling of the physiological and behavioral consequences of emotion as the cause for later disease. Since the "normal" outlet of the defense reaction, i.e. strenuous physical work during true flight or fight behavior, is inhibited during psychological stress, disruption of bodily homeostasis occurs. This may take the form of flushing the blood with energy sources like FFA, which, if unused, will be converted to cholesterol.[117, 567] Or it may act through the repeated surges in arterial blood pressure[181] , and the "overperfusion" of inactive muscle[429] , leading to lasting changes of the peripheral vascular resistance and a resetting of the baroreceptor set point. Stress may further hamper adequate blood pressure regulation by increasing renal vascular resistance that causes antinatriuresis with sodium retention, a decrease in glomerular filtration rate, and stimulation of renal renin release.[111] Furthermore, high plasma levels of noradrenaline and adrenaline, particularly in combination with cortisol, may be directly toxic to the heart vasculature[580, 22]

Since all adverse effects of stress are thought to depend crucially on the activation of the autonomic nervous system and subsequent physiological responses, measurement of individual differences in coping with stress has concentrated on measuring differences in physiological stress-reactivity. Various standardized tasks have been used to induce psychological strain in the laboratory, including the Stroop color-word conflict task[561] , mental arithmetic, memory search tasks, video games, general knowledge quizzes, and items from adult IQ scales. These mentally taxing tasks are made distressing by forcing the subjects to comply with pre-set criteria for accuracy and reaction time. Failure to meet these criteria leads to harassment by a laboratory confederate, or is punished by loud noise bursts or electric shocks. Alternatively, the tasks are made emotionally challenging by leading the subjects to believe that performance was monitored publicly (e.g. video camera), that their intelligence is being measured, or by head-to-head competition for a substantial financial bonus. Finally, laboratory stressors include various affective

conditions, like speeching before peers, role-playing, upsetting movies, and interviews of a stressful nature (e.g. the type A structured interview). These laboratory manipulations have been shown to evoke replicatable patterns of physiological activation, closely resembling the defense reaction seen during real-life stress-situations. Individual differences in stress-reactivity of the various physiological parameters are quantified by computing the task-induced increases above the resting baseline level. Baseline levels are obtained during quiet rest before or after the stressors, or even during a separate session.

Heart rate and blood pressure are the parameters most often measured, followed by fluctuations in electrodermal activity, respiration rate and the release of (nor)adrenaline and cortisol in urine. However, since many tasks are laboratory-based, more complex measurement of the autonomic nervous system response is possible. Impedance-cardiography allows for the non-invasive determination of cardiac contractility as well as an estimation of cardiac output[512] and the vascular resistance of the total body or separate limbs.[5] Catheterization of the forearm in combination with a blood-withdrawal pump allows continuous sampling for plasma adrenaline and noradrenaline as well as for a host of other blood borne indicators of stress like FFA, glucose, ACTH, cortisol and β-endorphin.[399] Detailed information on regional sympathetic nervous system activity is obtained from direct measurement of muscle vasoconstrictive nerve activity[600] or from the product of arterial to venous noradrenaline gradients and regional blood flow.[153] Simultaneous recording of ECG and the respiratory signal can be used to compute an index of cardiac vagal activity.[222] The recent introduction of non-invasive continuous blood pressure monitoring further allows computation of short term heart rate and blood pressure variability and baroreflex sensitivity.[413]

A striking finding in many of the studies on the physiological stress response, is the large individual difference in the amplitude and patterning of the response, even to a highly standardized laboratory stressor. Over the past decade, exaggerated reactivity, particularly cardiovascular reactivity, has come to be considered as an independent risk indicator for future hypertension, hypertensive complications, atherosclerosis and CHD.[497, 372, 385] Clearly, stress reactions will only lead to cardiovascular disease when they are prolonged (prevailing state), or occur very often (recurrent activation).[372] Therefore, the validity of individual differences in laboratory stress-reactivity depends critically on their correspondence to physiological activation seen in real-life stress situations. To date, stress-reactivity still awaits true confirmation as an independent CHD risk factor in large scale longitudinal studies, as has been performed for the conventional risk factors. However, the accumulated data, particularly from animal research, point to the physiological plausibility of a direct effect of hormonal and cardiovascular reactivity on health.[497, 385] Cross-sectional data in humans further support this, since hormonal and cardiovascular hyperreactivity to stress is more prominent in subjects with borderline hypertension[190] , familial history of hypertension[373, 192] and type A behavior[91, 610] , characteristics that have all been associated with increased risk for CVD. Furthermore, evidence from longitudinal studies suggest that simple heart rate and blood pressure reactivity predict future atherosclerosis[371] and hypertension.[396, 162] Therefore, research has concentrated on finding the determinants of hyperreactivity to stress, and possible ways to change it. Aerobic fitness is increasingly named as one such

factor influencing stress-reactivity. It is specifically hypothesized that high fitness is associated with low reactivity. The next paragraph will review the evidence for such a connection.

4. Aerobic fitness and stress-reactivity

At face value, the idea that fitness influences stress-reactivity is a plausible one, and based on a simple analogy. Fit persons adapt more efficiently to a physical workload. The sympathetic effects of a fixed submaximal exercise level are smaller in high fit subjects and in response to the same workload they show less heart rate acceleration and vasoconstriction in non-working tissue.[621] Probably as a consequence of the latter, the noradrenaline response to exercise is also smaller in the high fit.[434] Because the stress response is predominantly sympathetic in origin and the same physiological systems are involved, a smaller physiological reaction to stress could also be expected in high fit persons. This idea has enormous potential, since it suggests that the link between stress and disease could be broken by increasing one's fitness through regular exercise. However, the resemblance of the response to exercise and emotional stress is only superficial. During exercise the autonomic nervous system activity is controlled by feed-forward from central (motor) command centers as well as feedback from muscle afferents.[483] Virtually no muscular work takes places under stress, and the autonomic nervous system activity largely reflects central command. This has consequences for the comparison of trained and untrained subjects. Studies comparing submaximal exercise performed with trained and nontrained muscle groups (e.g. one leg training, or arm cranking versus bicycling), have shown that the fall in submaximal heart rate is confined to exercise with trained muscles.[87, 493] Similarly, the vasoconstrictive action in non-working areas may be smaller in trained subjects only when they work with trained muscles.[87] The training effect on sympathetic outflow to non-working tissue appears to be linked to the enhanced O_2-extraction of trained muscles, that have lesser need to trigger extensive sympathetic re-distribution of blood away from non-working areas. This suggests that afferent feedback from metabolism or muscular activity may be necessary for training-related adaptations to show. No such cues are present during stress, where cardiovascular responses occur without noticeable changes in muscular activity. Thus, it would be unwise to expect fitness to reduce sympathetic reactivity to stress, simply based on on an analogy with the response to exercise. Instead direct empirical proof of reduced stress-reactivity in the fit is needed.

Fitness and stress-reactivity: empirical evidence

The relationship between fitness and stress-reactivity has been under study for about 10 years. In this period at least 30 studies have been published, covering the responses of 1160 male and 321 female subjects. Table 1 presents these studies in the order of publication date. A summary of the most important elements of all studies is given, including the findings on physiological stress reactions and, when measured, the recovery from the stressor.

Table 1: Summary of studies on stress and fitness.

Study	Population			Grouping		Design		Outcome		
	Subjects	Number & Sexe	Age	Selection & Fitness/Activity Assessment	Fitness Differences	Stressors	Physiological Variables	Baseline	Reactivity[a]	Recovery
Raab & Krzywanek 1965	Working men	108 M	43.0 (± 9.2)	Upper vs Lower quartiles of habitual activity levels	n.m.	Memory Search task	SBP,DBP,HR,	HR↓	no differences	no differences
Cantor et al. 1978	Students	36 M, 36 F	17 - 20	Median Split on SBP-Recovery after short bicycle exerc.	n.m.	2 Stressful Films	SBP,HR, Skin temp.	n.m.	SBP↓, Skin temp.↓	n.g.
Cox et al. 1979	Students	41 M, 29 F	18 - 26	Correlational VO_2-max assessed with submax. bicycle exerc.	mean: 37.3 $ml.kg^{-1}$	Stroop-conflict	HR	HR ↓	no differences	HR↓
Zimmerman & Fulton 1981	Students	40 M	19 - 42	Selection of Runners vs Sedentary verified with Cooper's points	7 vs 196 points	RAVEN's IQ-test	HR, GSR	HR↓	no differences	no differences
Sinyor et al. 1983	Students	30 M	20 - 30	Selection of Heavy vs No training. VO_2-max from submax. bicycle exerc.	69.1 vs 32.8 $ml.kg^{-1}$	Quiz, Mental Arithmetic, Stroop-conflict	HR, E, NE, Cortisol in plasma	HR↓, Cortisol↑	no differences	HR↓
Dorheim et al. 1984	Unspecified	24 M	29 - 53	Selection of Marathoners vs Untrained	n.m.	Video Game, Cold Pressor, RT-task	SBP,DBP,HR SV,TPR, NE,E, Cortisol in plasma	HR↓, SV↑	no differences	no differences
Hollander & Seraganian 1984	YMCA members	10 M, 9 F	35 - 45	Selection of Recently Trained vs Untrained. VO_2-max from the step test	n.g.	Mental Arithmetic	HR, SCL	HR↓	no differences	HR↓, SCL↓
Hull et al. 1984	Unspecified	35 M, 20 F	21 - 64	Quartiles of max. treadmill endurance times during the Bruce protocol	<12 vs 12-15 vs 15-18 vs >18 min.	Stressful Film Stroop-conflict, Cold Pressor	SBP,DBP,HR, E,NE in plasma	HR↓, older: SBP↓	older:DBP↓	older: DBP↓
Keller & Seraganian 1984	YMCA members	39 M	20 - 50	Selection of Athletes, Trainers, and Untrained. VO_2-max from the step test	n.g.	Stroop-conflict, Tracking task	EDR	n.m.	n.m.	EDR↓
Holmes & Roth 1985	Students	20 F	17 - 31	High vs Low Septiles of VO_2-max assessed with submax. bicycle exerc.	53.5 vs 28.8 $ml.kg^{-1}$	WAIS' IQ-test	HR	HR↓	HR↓	no differences

a) Reactivity differences limited to one task/age-group only, are indicated separately. Otherwise results apply to all tasks/age-groups.

(table 1 continued)

Study	Population			Grouping		Design		Outcome		
	Subjects	Number & Sexe	Age	Selection & Fitness/Activity Assessment	Fitness Differences	Stressors	Physiological Variables	Baseline	Reactivity	Recovery
Lake et al. 1985	Students	73 M	18 - 24	Selection of Athletes vs Sedentary. VO_2max from the step test	60.0 vs 42.0 $ml.kg^{-1}$	S.I.,Card Game, Snakes,CP, Ment.Aritm.	SBP,DBP,HR,	HR↓,DBP↓	SI:SBP↓,DBP↓ CG:DBP↑,MAP↑	n.m.
Perkins et al. 1986	Hypertensive patients[b]	18 M	21 - 63	Selection of Recently Trained vs Untrained	n.m.	Video Game, Ment.Aritm.	SBP,DBP,HR	no differences	VG:SBP↓,DBP↓	n.m.
Shulhan et al. 1986	Students	24 M	24.5	Median Split on VO_2max assessed with the step test	54.6 vs 44.0 $ml.kg^{-1}$	Ment.Aritm.	HR, TWA-red	no differences	TWA-red↓	n.m.
Brooke & Long 1987	Students	26 M	26.0 (±3.3)	Median split on VO_2max from max. Treadmill exerc. (pre-selected high/low active)	48.0 vs 58.0 $ml.kg^{-1}$	Rappelling	HR, NE, E, Cortisol in plasma	HR↓	no differences	E↓
Holmes & Cappo 1987	Students with FH+[c]	21 M	n.g.	Median Split on VO_2max assessed with Submax. bicycle exerc.	50.1 vs 26.9 $ml.kg^{-1}$	Ment.Aritm., Stroop-conflict	SBP, DBP, HR	n.g.	SBP↓,DBP↓, HR↓	n.m.
Holmes & McGilley 1987	Students	76 F	17 - 20	Median Split on habitual activity levels verified with the Cooper test	1.49 vs 1.00 miles in 12 min.	WAIS' IQ-test	HR	HR↓	HR↓	n.m.
Jamieson & Lavoie 1987	Students	56 M	21.5	Correlational. VO_2max from max. bicycle exerc.	mean: 49.8 $ml.kg^{-1}$ range:30 - 75	Stroop-conflict	HR	n.g.	no differences	no differences
Light et al. 1987	Students	170 M	18 - 22	High, Moderate, Low activity levels assessed with Cooper's aerobic points	0-19 vs 20-63 vs >63 points	RT-task, ColdPressor	SBP, DBP, HR,PEP-red	HR↓, DBP↓	RT: HR↓, SBP↓, PEP-red↓	n.m.
Plante & Karpowitz 1987	Students	107 M	17 - 30	Intense,Moderate,No physical activity assessed with Cooper's aerobic points	15 vs 49 vs 119 points	Electric Shocks, IQ-test	HR, PV, SCL	HR↓, PV↓	no differences	Shocks: HR ↓
Sothmann et al. 1987	Local residents Milwaukee (trait-anxious)	19 M	35 - 50	High vs Low Septiles of VO_2max from max. Treadmill exerc.	44.6 vs 65.4 $ml.kg^{-1}$	Stroop-conflict SBP, DBP	HR, E, NE in plasma	HR↓, DBP↓	NE↓	n.m.

b) To rule out effects of hypertensive status, only comparisons between fit and unfit hypertensives were used; data from normotensives were discarded.
c) To rule out effects of familial background, only comparisons between fit and unfit subjects with a familial history of CVD were used.

(table 1 continued)

Study	Population			Grouping		Design		Outcome		
	Subjects	Number & Sex	Age	Selection & Fitness/Activity Assessment	Fitness Differences	Stressors	Physiological Variables	Baseline	Reactivity	Recovery
Turner et al. 1988	Students	24 M	21.3	Selection of Trained vs Untrained. VO_2max from submax. bicycle exerc.	75.0 vs 51.8 ml/kg	Video Game Mental Arithmetic	SBP, DBP, HR	HR↓	HR↓	n.m.
Claytor et al. 1988	Students	34 M	n.g.	Median Split on stress-reactivity. VO_2max from max. treadmill exerc.	mean: 48.2 ml/kg	RT-task, Electric Shocks	SBP, DBP, HR	n.m.	no differences	n.m.
Claytor et al. 1988	Students	16 M	21.7 (±1.8)	Selection of Athletes vs Sedentary. VO_2max from max. treadmill exerc.	45.5 vs 70.6 ml/kg	Cold Pressor, RT-task	SBP, DBP, HR, A, NA in plasma	HR↓	no differences	n.m.
van Doornen & 1989	Students	15 M	18 - 26	Selection of Atheletes vs Sedentary. VO_2max from submax. bicycle exerc.	48.9 vs 67.2 ml/kg	RT-task	SBP, DBP, HR, PEP, CO,TPR	HR↓ DBP↓	PEP↓, HR↓, DBP↓, TPR↓	n.m.
Long 1990	University Community	54 F	18 - 48	Median Split on VO_2max assessed with submax. bicycle exerc.	<45.0 vs >45.0 ml/kg	Quiz, Mental Arithmetic	SBP ,DBP ,HR, A, NA, Cortisol in plasma	HR↓, DBP↓	DBP↓	HR↓, NA↓
Steptoe et al. 1990	Local Residents (London)	20 M, 55 F	18 - 60	Median Split (all Sedentary) on VO_2max assessed with submax. bicycle exerc.	29.1 vs 40.2 ml/kg	RAVEN's IQ-test	SBP, DBP, HR,	HR↓, RR↓ RR,Vt,SCL	RR↓	SCL↓
Czajkowski et al. 1990	Military Officers	62 M	42.0	High vs Low Quartiles of max. treadmill times during the Bruce protocol	>14.2 vs <11.8 min.	S.Interview Video game Mental Aritm.	SBP, DBP, HR	HR↓, DBP↓	VG:HR↓, DBP↓	n.m.
Houtman & Bakker 1991	Inexperienced Teachers	17 M, 22 F	25.1 (±2.5)	Correlational. VO_2max from submax. bicycle exerc.	n.g.	Lecture	HR, cortisol in saliva	n.g.	men: HR↓	no differences
Sothmann et al. 1991	Unspecified	52 M	39.5 (± 1.2)	High, Moderate, Low Fit subjects n.g.	60.0 vs 40.0 vs 30.0 ml/kg	Stroop-conflict	NA, A in plasma	no differences	NA↓	n.m.
Claytor 1991	Students	43 M	20.9 (±0.4)	Selection of Highly Trained vs Normally Fit. VO_2max from Max. Treadmill	49.0 vs 68.2 ml/kg	Stroop-conflict, IQ-test, Mental Aritm.	MAP, HR, FBF CO, SV, TPR, Ve A, NA in plasma	HR↓	no differences	n.m.

n.m. **indicates that an outcome variable was not measured, and** ***n.g.*** **means that the outcome was not given in the paper.**
Further abbreviations: M = Male, F = Female, Stroop-conflict = Stroop word color conflict task, WAIS = Wechsler Adult Intelligence Scale, S.I(nterview) = type-A Structured personal Interview, Snakes = live snake presentation, RT(-task) = Reaction Time task (with threat of shocks or loud noise bursts), RAVEN's IQ test = RAVEN's Progresive matrices (spatio-visual ability), CP = Cold Pressor test, HR = Heart Rate, SBP = Systolic Blood Pressure, MAP = Mean Arterial Blood Pressure, DBP = Diastolic Blood Pressure, Skin temp. = Skin temperature, GSR = Galvanic Skin Response, SCL = Skin Conductance Level, EDR = Electrodermal Activity Ratio, NA = Noradrenaline, A = Adrenaline, SV = Stroke Volume, CO = Cardiac Output, TPR = Total Peripheral vascular Resistance, PV = blood Pulse Volume, TWA-red = T-wave Amplitude reduction (beta-adrenergic cardiac drive), PEP = Pre-Ejection Period (beta-adrenergic cardiac drive), RSA-red = Respiratory Sinus Arrhythmia reduction (loss of vagal cardiac drive), FBF = Forearm Blood Flow, RR = Respiration Rate, Vt = Tidal Volume, Ve = Minute Ventilation.

At least two-thirds of the subjects used were students, but several samples from the working population have also been studied. Most authors aimed to compare groups with different levels of aerobic fitness. However, strategies to select such groups were wildly diverse. Sometimes extreme groups were selected based on differences in sports behavior (highly-trained athletes vs sedentaries). At other times groups were selected on the basis of questionnaires for habitual physical activity (median split or extreme groups), or on the basis of their fitness level assessed with a (sub)maximal exercise test (median split, high/low quartiles, or high/low septiles). Still other studies looked at the direct correlation between fitness level and stress-reactivity within a group of subjects. Levels of habitual activity or training state were often not systematically assessed, particularly when fitness was used as a grouping criterion. Only a few studies used detailed questionnaires or the Cooper's aerobic point system[93] to quantify differences in habitual activity level. Luckily most of the recent studies assessed the maximal oxygen consumption of their subjects, although the methods to do so varied widely. Both submaximal and maximal protocols were used, and exercise tests consisted of the step test, bicycle ergometry or treadmill running. Treadmill endurance times during the standard Bruce protocol[65] were sometimes given as an alternative to Vo_{2max}.

Slightly more consistency was found in the measurement of stress reactions. Nearly all studies used short-term laboratory stressors to evoke a stress response in their subjects. Most often mental stress tasks were used: the Stroop color-word-conflict task, reaction time tasks, mental arithmetic IQ tests or video games. In some studies the cold pressor test (immersion of a hand in ice water) was used, which combines psychological with physical stress. Different subsets of physiological variables were measured across studies, but all are known to index the presence of the same "fight-flight" reaction.

The heart rate response

Twenty eight studies measured heart rate in high and low fit groups. As was to be expected, a far majority of studies observed lower baseline heart rate in fit subjects (indicated by a down aroow in the table). Only 3 out of the 24 studies presenting baseline heart rates observed no difference between groups. Twenty studies did not find a difference in heart rate response to the laboratory stressors (negative studies), and 8 observed smaller responses in high-fit subjects (positive studies). So, 29 % of the studies observes a difference in the expected direction. This may even be a too optimistic estimate. About half of the studies presented more than one stressor to the subjects. The 28 studies tested the response to a total of 53 task presentations. The studies reporting negative results generally didn't find the effect in any of the tasks presented. The studies that did report fitness effects found the heart rate response to be lower in only one of their tasks, but not in the others. Looking at the results in this way compromises the influence of fitness even more. Only in 10 out of the 53 task presentations (19 %) had the high fit subjects a smaller heart rate response than the low fit subjects. On the other hand: not once were the high fit subjects shown to have a larger stress-response.

In the studies reporting a significant fitness effect, the difference in fitness level of the high- and low fit group might have been larger than in the negative studies. I checked

this possibility for those studies in which aerobic fitness was estimated or explicitly measured as the maximal oxygen uptake. In the negative studies the average Vo_{2max} levels of the high- and low fit groups were 60 and 43 $ml.min^{-1}.kg^{-1}$ (based on 7 studies); in the positive studies these values were 62 and 39 respectively (based on 4 studies). So it seems unlikely that the size of the fitness difference between the groups could explain the different result of the positive and negative studies. Another possibility is that the strength of the stressor, i.e. the magnitude of the response, determined the chance of finding a difference between groups. In as far as studies explicitly presented data about the average task response, or allowed an estimate of the response from figures, the median heart rate response was found to be 10 bpm in the negative, and 15 bpm in the positive studies. This suggests that only the stronger stressors will create a difference between high- and low-fit subjects. The picture, however, is far from consistent. Some studies using stressors that evoked a strong response (e.g. Cox et al.[94] , about 33 bpm and Claytor et al.[88] 25 bpm) didn't find a difference between high and low fits, whereas studies with rather weak stressors (van Doornen & de Geus[130] , 5 bpm and Turner et al.[584] 9 bpm) did find a difference between high and low fits. Although it is clear that if a stressor hardly evokes a response there is little chance of finding a group difference, the difference in response amplitude can only partly explain the difference between positive and negative studies.

It has been hypothesized that fitness does not so much affect the responsiveness, but in contrast helps the organism to recover more quickly once stress has subsided. Such recovery has been measured for the heart rate as the increase above baseline values still present at 2 to 30 minutes after the (last) stressor. Out of the 14 studies measuring heart rate recovery from stress only 4 (29 %) found a faster/fuller recovery found in the high fit subgroup.

Three studies specifically assessed indices of sympathetic cardiac drive (Pre-ejection Period, T-wave amplitude). All three times, the stress-induced increases in sympathetic drive were found to be lower in fit subjects. In two studies this was paired to a lower heart rate response. No study measured the influence of fitness on the stress-induced reduction in vagal tone.

The blood pressure response

Sixteen studies measured blood pressure in addition to heart rate. Fourteen of them reported baseline values. Resting systolic blood pressure generally did not differ between high and low fit/active subjects (excepting Hull et al. 1984[265] who reported lower systolic blood pressure in a subgroup of fit older subjects). In contrast, 6 studies reported a significantly lower baseline diastolic blood pressure in fit subjects. Out of 16 studies 5 (31 %) reported a smaller systolic blood pressure reaction to a laboratory stressor in fit subjects, Again, this difference was often found for one of the tasks only, but not for all task(s) presented. In 6 out 35 task presentations (16 %) fit subjects showed a smaller systolic blood pressure reaction. The results for diastolic blood pressure responses were hardly better. Six out of 15 studies (40 %) observed smaller reactions in fit subjects. In 8 out of 34 task presentations (24 %) fit subjects showed a smaller diastolic blood pressure

reaction. Faster recovery of blood pressure was found only once and the effect was limited to the diastolic blood pressure in a subset of older subjects. Again, the reverse finding of higher reactivity in the fit subjects was not reported, with one notable exception. During a highly competitive card game Lake et al.[324] observed a higher blood pressure response in the fit subjects. In the same study however, these fit subjects had lower blood pressure responses to a stressful interview.

The height of the fitness differences between the groups did not seem to influence the chance of finding a group-difference in diastolic blood pressure response. However, the duration of the stress session, as well as the magnitude of the blood pressure response, appeared of some importance. In general, studies reporting an effect of fitness used multiple tasks or tasks of longer duration that evoked blood pressure reactions over 7 mmHg. Furthermore, when multiple mental stress tasks were presented, only the tasks yielding the highest blood pressure reactions showed fitness effects.[265, 324, 448, 102] Several studies have shown that during long term exposure to stress control over the blood pressure reaction shifts from the heart to the vessels.[401, 400, 76] Perhaps, a strong vascular component is needed before an effect of fitness on the blood pressure reaction shows up.

Other response systems

In addition to the cardiovascular parameters, 9 studies assessed the increase of adrenaline and noradrenaline levels in plasma or saliva during or after stress. Stress-induced increases in noradrenaline levels were twice found to be lower in the fit subgroup. The adrenaline responses never differed, although faster recovery to baseline in the high fit was mentioned once. Cortisol responses were measured 5 times, but again a group difference was never found, neither in reactivity nor in recovery. Although these variables are notably difficult to interpret, this suggests that the hormonal component of the stress-response is not related to fitness. Several other variables have been measured, including respiratory parameters (respiration rate, tidal volume, minute ventilation, oxygen consumption), electrodermal activity (Galvanic Skin response or Skin Conductance), skin temperature and finger pulse volume. The only reproducible result regarding these parameters was a quicker recovery of skin conductance levels after stress.

Performance

Many of the stressful tasks required substantial effort. Various strategies were used to increase the subjects' performance motivation. Subjects sometimes competed for a financial bonus[448, 584, 130, 88] or were led to believe that their performance would be compared to peer group norms[352, 271] or evaluated by the academic staff.[453] At other times, punishment by loud noise[130] , electric shock[343, 88] , or verbal harassment[94, 619, 324] was made contingent on task errors or slow reaction time. However, a direct effect of fitness on task performance was seldom tested. Only 6 out of 32 studies tried to assess whether the fit subjects performed better than the unfit (or vice versa) and whether this influenced reactivity.[522, 448, 513, 538, 343, 130] Only 2 of these 6 studies reported better performance in the high fit subjects[448, 538] , but this does not exclude

the occurrence of such effects in the 26 remaining studies that did not account for them. Differences in the performance of high and low fit subjects might signal differences in task ability and/or task involvement. These could interfere with the interpretation of the between-group differences in reactivity as indicative of differences in psychophysiological stress-resistance.

Reactivity and Level

A serious problem hampering comparison of the studies in table 1 is the dependency of reactivity on base levels. For example, low initial heart rate levels are thought to lead to higher heart rate responsivity (the "Law" of Initial Values).[323] Such an inverse relationship between a variable's responsivity and its baseline may cause an overestimation of reactivity in the high fit subjects, because they often have low basal heart rates. About half of the studies have used analysis of covariance to get around this phenomenon and to create a measure of "true responsivity". In short, this means that the changes in heart rate reactivity under stress are corrected for the level of heart rate at rest. I feel very uncomfortable with such procedures. In the case of fit versus unfit subjects, the differences in base level and reactivity may share a common physiological basis (e.g. lower vagal tone). Correction of such differences would throw away relevant information. To worsen things, the decision to use covariance is often based on the presence of baseline differences rather than on a true relationship between reactivity and baseline (almost no data were presented on such a relationship). If heart rate reactivity is inversely related to heart rate level, than covariance analysis would truly "favor" the uncovering of a lower response in the high fit. Yet, some studies suggest that both baseline heart rate and heart rate reactivity may be simultaneously lower in fit subjects.[252, 255, 343, 584, 130, 102] Covariance in this case, reduces the chance of finding a favorable fitness effect, instead of enhancing it.

The overemphasis on stress-reactivity itself, whether adjusted for baseline levels or not, tends to cloud the most relevant finding in all studies reviewed: In spite of the large differences in methodology, virtually all of the studies showed the absolute level of heart rate and blood pressure during stress to be lower in the high fit subjects. In figure 1 the relationship between heart rate levels during the stressors and aerobic fitness is presented graphically. There were 20 studies from which the relevant data could be extracted. The middle panel is based on studies quantifying fitness in Vo_{2max}. The heart rate levels of the low and high fit groups are plotted against their respective fitness levels. In the right and left panel, heart rate levels are given of studies categorizing their subjects in high and low fit/active without explicitly mentioning fitness levels. Figure 1 demonstrates yet another problem in the comparison of studies: what is called high fit in one study may be considered low fit in another. In spite of this problem, all studies systematically show a lower absolute heart rate level under stress in the high fit group than in the low fit group. Heart rate level under stress seems to decline with increasing fitness level. In most studies, the lower stress levels found in the fit group were a consequence of a lower resting heart rate. However, in some studies reactivity also contributed to the group difference found during stress. Furthermore, within studies some individuals were seen to lower

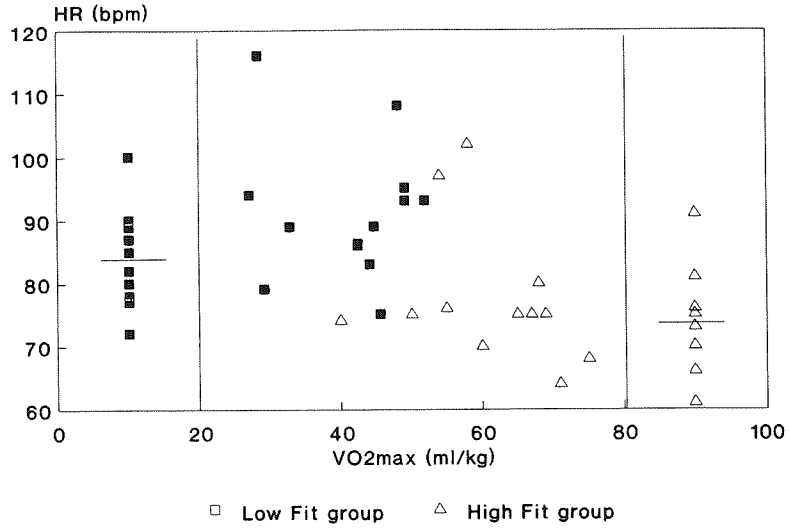

Figure 1: Average heart rate levels during stress in high fit and low fit subjects. In the middle panel the average heart rate of the low (square) and high fit (triangle) groups are plotted against the average fitness levels of these groups. Right and left panels give the heart rate levels in studies, that did not mention fitness level, but simply categorized their subjects in high and low fit groups. Combining both types of studies the average heart rate under stress was found to be 84.5 bpm in low fit groups and 73.8 bpm in the high fit groups.

their stress levels solely through lower basal levels, whereas others lowered both their reactions and basal levels. A similar picture can be drawn for the stress levels of diastolic blood pressure. Seven out of 14 studies found significantly lower absolute levels of diastolic blood pressure during stress in the high fit subgroup (and in four more the figures/tables suggested such effects, although no explicit testing was reported). Again the effect combined the lowering of stress-reactivity in some individuals with the lowering of basal levels in others.

These effects on the absolute levels of cardiovascular arousal also seems to hold up under conditions of more severe life stress, as was demonstrated by Schwaberger[502] , who found significant correlations of Vo_{2max} with heart rate level (r= -0.85) during a car race. In addition, fit subjects had lower heart rate level during rappeling[539] and public speaking.[260] Since it is unclear, at present, whether reactivity or levels are pathologically the most relevant, the finding that fit subjects consistently show lower levels during stress is an important observation, even if reactivity is not reduced.

Conclusions

An earlier quantitative meta-analysis by Crews and Landers of the effects of acute as well as chronic exercise on the response to short-term physical and psychological

stressors, suggested that about half of the studies had found lower reactivity in exercising subjects.[100] In the present review, focussing on the influence of aerobic fitness on the stress-reactivity to psychological stressors, only rudimentary quantification of study results was undertaken. There were enormous differences in study design (use of fitness versus activity to select groups, differences in the range of fitness and activity levels, type of tasks, incentive/punishment strategies, task-duration, timing of baseline measurements) and a number of studies presented only partial or graphical data. Even the most simple form of meta-analysis that was adopted in this review, computation of the ratio of positive and negative studies, must be interpreted with caution due to the inconsistent use of covariate analysis. Looking at the positive/negative study ratio, chances of finding lower reactivity in some variable in the high fit subgroups were about "fifty-fifty". However, when positive/negative ratios were counted per variable and per task, the true percentage of lower reactivity in the high fit appeared to vary from 16 to 24 %. Furthermore, the fitness effect was not very strong, i.e. large differences in fitness yielded only small differences in reactivity between the groups. Nonetheless, one cannot help being impressed by the fact that virtually none of the studies reviewed reported a higher stress-reactivity in fit/active subjects. That is, the fit and active were only once found to be more reactive.[324]

The above findings could easily be taken to indicate that fitness is associated with a beneficial reaction to stress, a conclusion that is often encountered in the discussion sections of the studies reviewed. However, some caution is in order. First of all, the failure to find (published) negative results may reflect a publication bias. This bias toward beneficial effects of fitness may reside on the side of editors and referees, but is more likely found at the level of the authors themselves, who may not be inclined to "believe" their own data if they are unexpected. Secondly, presentation of data was sometimes inadvertently biased, although the authors were acting in good faith. Holmes & Cappo[254] decided to analyze only 2 of the 5 tasks that were presented. The choice being based on the "effectiveness of inducing arousal". On those two tasks, high fits appeared to respond less than low fits. The responses, however, to the other tasks were not mentioned, and presumably no fitness effect was found. Czajkoswki et al.[102] discarded the results from the Structured Interview because "reactivity was to low", but again fitness effects are not given. In contrast, Lake et al.[324] analyzed only two out of five tasks, because they were "sensitive" to fitness effects, although reactivity to the non-analyzed tasks was substantial. Reporting only the tasks that showed a significant effect of the fitness dimension may distort reality and accidentally cause an overestimation of the effect. Apart from the selective focus on certain tasks only, one often finds mention of trends and near-significant effects in favor of a fitness effect, but the opposite is a rare event. Of course this does not necessarily reflect "wishful testing", but from a statistical viewpoint it is rather surprising.

Notwithstanding these possible biases towards the publication of beneficial fitness effects, it is justified to conclude that high fitness is associated with a favorable cardiovascular response to stress. Although lower reactivity was not consistently found to occur in a single variable, all variables measured tap the same general increase in autonomic arousal. Since it is the activity of the autonomic nervous system that is

hypothesized to mediate stress-induced disease, any sign of lower autonomic activity in the high fit should be regarded as an adaptation. Moreover, during stress, absolute heart rate and blood pressure levels were often found to be lower in the high fit subjects. This is a highly desirable outcome. It reduces, for instance, the load on the heart. Myocardial work load is often expressed as the product of systolic blood pressure and heart rate. In the studies reviewed, reports of lower basal levels of heart rate and systolic blood pressure, lower systolic blood pressure reactivity, lower heart rate reactivity, or lower stress levels of heart rate and systolic blood pressure, were all taken to indicate a lower cardiac work load under stress. Using this definition, 25 out of 30 studies (84 %) suggested lower myocardial work load during stress in the fit group (in 12 of these heart rate and/or systolic blood pressure reactivity contributed). Such results make it safe to say that the fit subgroups in table 1 were much better equipped to deal with the physiological consequences of stress than their less fit counterparts.

The need for additional research

The above conclusions closely reflect the state of the art in 1988, when the experimental work for this thesis was started. The cross-sectional comparison of high and low fit subjects was certainly encouraging. It suggested that increases in fitness through regular exercise could be an effective way to reduce the risk for stress-related disease. If taking up exercise would reduce some aspect of stress-reactivity in about 50 % of the cases that would be a marvelous result indeed! However, some serious concerns remained. The bulk of the studies compared subgroups of highly endurance trained to completely sedentary subjects. This should immediately caution us against overenthusiastic expectations regarding the effectiveness of newly started training programs. Although aerobic fitness can be successfully manipulated through intensive exercise, progress in fitness after 2 to 6 months of training generally is no more than 10-30 %.[621] In comparison, the difference in aerobic fitness between the endurance trained and sedentary subjects used in the cross-sectional studies was often as large as 100 %. The high level of aerobic fitness of the endurance trained may follow from their long-term exercise habits (often several years), but they may also reflect a favorable genetic make-up.[47, 158] In fact, even the increase in fitness in response to regular exercise, i.e. the trainability of the subject, appears to vary strongly between individuals.[460] Since individual differences in stress-reactivity may also have a partial genetic basis[122, 257] , it is entirely possible that high fitness and low stress-reactivity go back on the same set of underlying genetically determined traits. In that case, training may completely fail to reduce stress-reactivity, even if it would improve fitness, because the underlying "third factor" had not been altered. In short, a causal effect of exercising on stress-reactivity through improved physiological make-up cannot be inferred from the cross-sectional comparison of exercisers with non-exercisers. Before regular exercise is recommended to counter stress, experimental training studies should first establish a direct influence on the physiological responses to stress.

A second concern with the studies reviewed is their reliance on heart rate, blood pressure, and the catecholamines as the main indices of stress-reactivity. Changes in

heart rate during stress depend on a combination of reduced vagal tone[222, 5] and increased sympathetic drive.[510] Since fit subjects are reported to have higher vagal cardiac control[146, 299] it may be interesting to see whether high vagal tone, rather than diminished cardiac sympathetic drive explains the low heart rate reactivity and faster recovery sometimes found. Furthermore, heart rate reactivity may be less important than the cardiac output response. A well noted improvement in cardiovascular efficiency of fit subjects is their larger stroke volume, which allows heart rate to be lower during resting and submaximal exercise conditions without jeopardizing cardiac output.[621] There is every reason to be cautious with the interpretation of a lower heart rate response to stress as a "healthy" response, since the advantage will depend largely on how the stroke volume behaves. If a smaller heart rate increase of a high fit subject is not paralleled by a larger decrease in stroke volume, then the resulting changes in cardiac output may not be different from that of a less fit subject with a higher heart rate response. The rise in cardiac output may be far more relevant than the increase in heart rate, since increased cardiac output acutely causes tissue overperfusion or an increase in arterial blood pressure. Catecholamine levels in urine or blood also fail to index important differences between low and high fit subjects. Noradrenaline levels at best reflect overall sympathetic activity, but the effect of fitness on the contribution of different tissues is unclear. Low noradrenaline levels may represent reductions in either muscular or non-muscular vasoconstriction, but may also reflect decreased cardiac drive. Adrenaline appears to be a more direct index of sympathetic activity, since it is released from the adrenal medulla only. However, fitness-related differences in target organ efficiency may severely limit the interpretation of adrenaline levels. For instance, fit subjects are characterized by enhanced vasodilatory responsiveness of the muscles to adrenaline[564] , which is probably related to increased sensitivity of the β-2-receptors. Therefore, similar adrenaline release during stress may give rise to larger vasodilation in the fit subjects, and in turn reduce diastolic blood pressure reactivity.[130] In short, the cross-sectional studies reviewed in this chapter may not have concentrated on the most relevant parameters. Additional research was needed focusing on differences in the cardiac sympathetic / parasympathetic balance and on the cardiac versus vascular contribution to the increased blood pressure during stress.

Finally, the use of selective recruitment of sporters vs non-sporters in the studies reviewed further complicated their interpretation. Participation in sports may attract only a limited set of persons with a specific psychological make-up. Large-scale population studies suggest that regular exercisers have good mental health, are highly self-motivated and emotionally stable.[548, 312, 560] In contrast, hyperreactivity to stress has been found more prominent in subjects with high scores for type A behavior, anxiety, and hostility.[385, 197] One could attribute the lower stress-reactivity of regular exercisers to superior psychological coping with stressful situations, instead of attributing it to increased aerobic fitness. This would, of course, be less worrisome if the favorable psychological make-up of exercisers was predominantly caused by exercising itself, as has sometimes been suggested.[488] However, it remains controversial whether a physical active lifestyle enhances psychological well-being, or whether happy, relaxed and non-depressed individuals simply have the vigor and energy to be active.[262] Subjects

who are exempted from stress because of a favorable psychological make-up or a desirable social economic position may, on the basis of the same psychological and social characteristics, also be more likely to get involved in leisure time sports behavior. In that case, the high incidence, among exercisers, of subjects who have both a desirable psychological profile and a low physiological stress-reactivity simply reflects self-selection. In summary, a causal effect of exercising on stress-reactivity through improved psychological make-up cannot be inferred from the cross-sectional comparison of exercisers with non-exercisers. Instead, the psychological effects of training should be measured in detail, and brought in direct relationship to the training effects on stress-reactivity.

The next two chapters report on two studies that were specifically designed to deal with the concerns raised above. In the first study, we improved on the physiological assessment of previous cross-sectional research, by including indices of cardiac β-adrenergic and parasympathetic tone, and the measurement of cardiac output and total peripheral resistance. The second study was set up as a replication of the first, and extended it by a profound assessment of psychological training effects. To separate the effects of aerobic fitness from those of exercise behavior, we used the fact that there are substantial individual differences in Vo_{2max} in a population with homogenous exercise habits (e.g. sedentaries). In a correlational analysis these pre-existing differences in fitness were compared to stress-reactivity. In addition, subjects were followed during a fitness training program, to test the possibility of changing stress-reactivity and psychological make-up through regular aerobic exercise.

5. Existing and training induced differences in aerobic fitness: their relationship to physiological response patterns during different types of stress

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Introduction

Regular physical activity during work or leisure hours has repeatedly been shown to be associated with a lower risk of coronary heart disease (CHD) in comparison to a more sedentary way of life (e.g.[436, 409, 492]). Several recent epidemiological studies suggest that the reduction in CHD risk may be explained by the high degree of aerobic fitness that generally accompanies regular physical activity[66, 414, 491, 531] Although regular exercise and aerobic fitness are both associated with a high HDL-C/LDL-C ratio and a low arterial blood pressure[616, 227] , high levels of physical activity appear to lower the risk of myocardial infarction even after correction for these major risk factors[126, 492, 35] To account for this phenomenon it has been suggested, in agreement with popular belief, that aerobic fitness training may attenuate the negative effects of psychological stress on cardiovascular health.

Numerous studies have claimed a beneficial effect of fitness training on psychological well-being, in terms of decreased feelings of anxiety and increased self-esteem[179, 37, 210] Furthermore, the efficiency of the cardiovascular system to deal with physical load is markedly higher in aerobically fit subjects, resulting in a reduced activation of the sympathetic nervous system during submaximal workloads. These positive psychological and physiological effects of fitness have led psychophysiologists to assume that high fit persons may evince smaller increases in sympathetic activity during psychological stress situations. Since the detrimental effects of stress are generally ascribed to repeated sympathetic reactivity and its concurrent effects on cardiac rhythmicity[593] , the vascular endothelium[86] , arterial blood pressure[181] , and lipid mobilization[150] , reduced stress-reactivity through increased fitness may form the basis on which exercise prevents daily stress to exert its negative influence on cardiovascular health.

Research to validate the assumption of lowered responsivity to stress in high fit subjects has been equivocal. About half of the studies have shown a reduced heart rate response to a variety of laboratory stressors[252, 584, 343, 254, 255, 130] whereas the other half did not find any differences between groups differing in fitness or exercise status.[522, 94, 133, 249, 265, 60, 538, 453] Moreover, no clear effects on venous plasma adrenaline or noradrenaline have been found, which directly contradicts the hypothesis of reduced sympathetic activity.[522, 265, 60] Sothmann et al.[538] observed a reduced noradrenaline response to a well-rehearsed vigilance task, but the use of high trait anxious subjects prevents generalization of this result. Clearly, differences in tasks used, gender, absolute fitness levels and more importantly, the operationalization of fitness may explain some of the equivocal findings. In addition, heart rate reactivity and catecholamine release may not have reflected the most salient effects of fitness: increased cardiac vagal tone[146] , larger stroke volume[621] , and greater vasodilatory

capacity.[564]

Much of the previous research on stress and fitness has compared groups that had a different activity status, i.e. exercisers vs non-exercisers. The problem with this approach is that these groups may have different psychological make-up, either because a selected set of people participates in exercise, or through psychological effects of exercise itself. Psychological differences may influence the appraisal of the stressor and one's coping-abilities and reduce emotional arousal. Using exercisers vs non-exercisers therefore, is not suited to detect the physiological effects of aerobic fitness per se. Empirically, a substantial variability in aerobic fitness has been shown in subjects that have been sedentary for many years.[414, 532] An alternative approach to study the effects of fitness on the stress response would be to use this variance in existing fitness levels of sedentary subjects in a correlational analysis. A direct test of maximal aerobic power on a treadmill or bicycle ergometer could then be used to determine aerobic fitness of these subjects. Such an approach would be useful to show that differences in stress-reactivity between high and low fit subjects are not a consequence of the effects of regular participation in sportive activities, or of the personality characteristics that may be selected together with the preference for sports. However, showing a cross-sectional relation between fitness and reactivity to stress, albeit interesting from a theoretical point of view, would be of little practical use, since it could mean that fitness and reactivity to stress are just two different markers of a healthy constitution. It seems important therefore, to test whether an increase in fitness through an exercise program can be used to influence the response to stress. This might prove helpful in modifying the stress response in groups suspected to have high sympathetic reactivity like type A persons or the offspring of hypertensive parents.

The present study measured the cardiovascular stress response in a group of young sedentary males, using indices of both cardiac and vascular reactivity. Three tasks were used that were ment to evoke either predominantly cardiac responses (Memory Search), combined vascular and cardiac responses (Tone Avoidance) and a predominantly vascular response (Cold pressor). During these tasks and in a five minute recovery period afterwards, we measured sympathetic (PEP) and parasympathetic (RSA) influences on the heart as well as stroke volume and the total peripheral resistance. We then looked at the correlations between physiological reactivity during the first confrontation with these tasks and the concurrent aerobic fitness status, determined by a maximal exercise test on a bicycle ergometer. During the following weeks a subset of the previously sedentary group participated in a program of endurance training of sufficient intensity to raise aerobic fitness. After seven weeks, the changes in reactivity to stress were compared to those of the remaining subjects who functioned as a waiting list control group and received training only after the experimental period. By combining the cross-sectional design with the longitudinal design we hoped to find out whether, in a sedentary population, aerobic fitness is associated with the response to stress, and whether a change in the response to stress could be brought about by endurance training.

Methods

Subjects

Subjects were 26 male students of the Free University of Amsterdam, with ages ranging from 18 to 28 (mean = 23.7). These subjects were recruited for a voluntary training program through advertisements in the campus magazine. The advert explicitly invited only those students that had performed no regular vigorous physical activity over the past year. Before admittance to the study, sedentary status of the students was checked by an activities interview. None of the original volunteers had to be rejected. The 26 subjects were randomly assigned to two groups. Sixteen subjects were to receive intensive aerobic training for the following seven weeks, whereas the other 10 were to receive their training after this seven week period. Two subjects, one from each group, were removed from the analyses because registration of physiological data was considered unreliable. Two more subjects, again one from each group, did not complete the second or third session, due to sickness (training group) or exams (control group). All remaining 14 subjects in the training group and 8 subjects in the waiting list control group participated to end. Subjects were paid 150 Hfl (82.5$) for their participation and received an additional bonus if they ranked within the top seven performers during the experimental reaction time tasks.

Experimental protocol

After recruitment, subjects performed a maximal exercise test and attended a laboratory session. The laboratory stress session and the maximal exercise test took place the same week, but always at least 24 hours apart. The laboratory sessions each lasted one hour. During the first session, subjects were made familiar with the general design of the experiment. They filled out the Spielberger trait anxiety inventory, that has been translated and validated for Dutch subjects.[455] Two reaction time tasks were explained to them and subjects practiced both tasks for several minutes.

During the experiment, subjects were comfortably seated in reclined position in a dimly lit, sound shielded, room. They faced a video monitor that was placed at three meters in front of them and used a panel with four buttons to respond during the reaction time tasks. After the electrodes and blood pressure cuff had been attached, subjects filled out the Spielberger state/anxiety inventory, followed by a ten minute resting baseline condition. They then had one minute of practice at a Memory Search reaction time task, followed by ten minutes of actually performing the task. After the task they sat quietly for a period of five minutes, denoted as the recovery phase. This procedure was repeated exactly for a Tone Avoidance reaction time task. The order of these tasks was the same for all subjects. After recovery from the Tone Avoidance reaction time task subjects sat quietly for three more minutes. They then were told to put their hand in ice cold water and keep it there for a period of one minute. Following this cold pressor test subjects remained seated for 15 minutes, during which, if they wished, they could read some magazines. They then had to sit quietly for ten more minutes, to obtain a post-stress level recording of all physiological variables. The post-stress condition ended the first

laboratory session. The second and third laboratory sessions, three and a half and seven weeks later, were identical to the first one.

Stressors

The psychophysiological stressors in this experiment consisted of two active coping tasks in which the subject had to respond both as accurately and as quick as possible in order to obtain a high score. The tasks were known to evoke two different patterns of cardiovascular reactivity. To prevent habituation, the tasks were made more demanding if the subject started to perform better. Motivation was kept high by a combination of feedback, competition and punishment. The scores were summed over both tasks and over all three sessions, and the seven subjects ranking highest after the last session were to receive a substantial financial bonus ranging from 100 Hfl (52$) for the best performance to 20 Hfl (10.4$) for the subject ranking seventh. These scores were kept on a large blackboard in the experimental room, visible to all subjects.

The first task was a memory search reaction time task that was based on the Sternberg memory search paradigm, and modelled after the task used by Schneider and Shiffrin.[496] Subjects had to memorize a set of three letters, that were presented on the video screen before the start of the task. Thereafter, sets of one to four letters were presented in which either none (50%) or one (50%) of the memorized letters would be present. Subjects had to respond as quickly as possible by pressing either the "present" or "not present" button. This response had to be delivered at least within 2000 msec to be considered correct. The faster they gave the correct answer the more points they gained. However, wrong answers led to a loss of points that was also linear with the speed of responding. After they had responded, they got immediate feedback on their performance in the form of a red (wrong), or green (correct) bar, that grew to the right (correct), or the left (wrong), proportional with the amount of points lost or gained. Digital feedback on the current total score was continuously present in the middle of the screen, even during presentation of the next set of letters. This set was presented almost immediately (300 msec) after the subject had reacted to the previous trial. The faster they responded therefore, the more trials they got over the ten minute period. During a pilot phase, this task had been shown to evoke relatively large increases in cardiac output and cardiac β-adrenergic drive (PEP).

The second task was a Tone Avoidance reaction time task. Subjects had to attend the occurrence of a stimulus (an 'X') that flared up shortly (500 msec) in one of the corners of the screen. They had to respond as fast as possible to this stimulus by pressing the knob opposite to this corner on their response panel. Incorrect or too slow responses were punished with a loud noise burst (1000 Hz,85 dB) that lasted 500 msec. Apart from the noise there was an extra penalty. After every two consecutive mistakes the original score of 3000 points was reduced by 100. However, if they made five consecutive correct responses, the score was increased by 50. The foreperiod varied randomly between 500 and 1500 milliseconds. Reaction time had to be shorter than a maximal response period, that was initially set to 550 msec, and was thereafter continuously adapted to the performance of the subject. This meant that, although the subject had constant contingent

feedback on his performance (fast responses avoiding the noise and gaining points), the actual score at the end of the task was about equal for all subjects. This task had previously been shown to evoke both an increased cardiac β-adrenergic drive, and an increase in vascular resistance.[129]

Number of correct responses, mean reaction time and total scores during both tasks were stored for later analysis. Stimulus presentation, blood pressure measurements and data acquisition were under control of a micro PDP11(DEC).

Signal recording

ECG Ag-AgCl electrodes were placed on the sternum and the lateral margin of the chest. ECG was recorded using an amplifier with a time constant of 0.3 sec and 1 Megaohm impedance. The impedance cardiogram(ICG) was recorded with an IFM Impedance Cardiograph (model 100) utilizing a tetrapolar aluminum band electrode system. The inner two measuring electrodes were placed around the base of the neck and around the thorax at the level of the xiphisternal point.[320] The current electrodes were placed 3 cm above and 3 cm below the measuring electrodes, imposing a current of 4 mA, with a frequency of 100 KHz. The first derivative of the impedance signal, $\Delta Z/\delta t$, was recorded with a time constant of 5 sec and a high frequency cut-off of 75 Hz. The respiration signal was recorded with a mercury strain-gauge strapped around the waist at a level 7 cm above the umbilicus. Frequencies above 30 Hz in this signal were removed by a hardware filter. The ECG, the $\Delta Z/\delta t$ and the respiration trace were displayed on a Beckman Dynograph (R611) and sampled continuously at 250 Hz using a DEC Micro PDP-11 in combination with a 12 bits AD-converter. Data were stored on RL02 disk for later off-line processing.

Signal processing

To get rid of artefacts both the ECG and ICG signal were filtered, using a low pass software filter with a 13.0 Hz cutoff. After this, the ECG and ICG complexes of each one minute period were ensemble averaged in reference to the ECG R-wave (see Muzi et al.[419]). The averaged complexes of the ICG and the ECG waves were used to compute the pre-ejection period (PEP), the left ventricular ejection time (LVET), and the maximal rate of change of impedance ($\Delta Z/\delta t$-max). PEP is an index of cardiac contractility[422] , and changes in PEP during stress are considered to reflect predominantly β-adrenergic effect on the heart.[510] $\Delta Z/\delta t$-max and the LVET can be used to calculate Stroke Volume using the formula proposed by Kubicek et al.[320] :

$$SV = \rho * (L_0/Z_0^2) * \Delta Z/\delta t\text{-max} * LVET.$$

In which ρ is resistivity of the blood at 100 K Hz, L_0 the shortest distance between the inner two (measuring) electrodes, and Z_0 the basic thoracic impedance that was read from a display on the impedance cardiograph at the start of each experimental condition. Blood resistivity (ρ) was set to a constant value of 135 Ohm, since in vivo experiments have shown this to be as adequate as estimations using the hematocrit value .[461] Cardiac output (CO) can be computed from the SV, by multiplying SV with the heart rate

(HR). Satisfactory correspondence has been shown between CO derived from impedance cardiography and CO assessed with the dye-dilution technique in rest and exercise.[108]

In the averaged ICG and ECG complexes, PEP, LVET, $\Delta Z/\delta t$-max and HR were defined as:

PEP: Time in msec between Q-wave onset in ECG and B-point in $\Delta Z/\delta t$ signal.

LVET: Left ventricular ejection time (msec), defined as the time between B- and X-point in the ICG.

$\Delta Z/\delta t$-max: The maximal rate of change in impedance, defined as the difference between the maximal amplitude of $\Delta Z/\delta t$ and the amplitude of the $\Delta Z/\delta t$ signal at the B-point.

HR: The time between successive R-waves expressed as beats per minute (bpm).

Since ICG and ECG complexes were averaged over one-minute periods, PEP,LVET,SV and HR scores represent mean minute values.

Blood pressure was measured every two minutes with a Dinamap Vital Signs Monitor (Critikon model 845 XT). It uses an oscillometric method to measure the mean arterial pressure (MAP), systolic (SBP) and diastolic (DBP) blood pressure. Combining the blood pressure measurements with the CO value of the corresponding minute, total peripheral resistance (TPR) could be estimated by the formula:

$$TPR = (MAP/CO) * 80 \text{ (in dyne-seconds/cm}^5\text{)}$$

From the respiration signal we computed the Total Time Expiration (TTE) as the sum of the expiration period and expiratory pause, the Total Time Inspiration (TTI) as the sum of the inspiration period and the inspiratory pause and Total Cycle Time (TCT) as the sum of all four intervals. TTE, TTI and TCT of a number of breaths were averaged to obtain mean minute values. Breaths that fell partly into two different minute periods were used in the averages of both minutes. Respiration Rate (RR) was computed as the mean total cycle length in a one minute period and expressed as cycles per minute(cpm).

Respiratory Sinus Arrhythmia (RSA) was computed using the peak-to-through method (for details see Grossman & Wientjes[221]). This method combines the respiratory time intervals and the RR intervals to obtain the shortest inter beat interval during the inspirational phase (which was made to included 1000 milliseconds from the following inspiratory pause/expirational phase) and the longest inter beat interval during expiration (including 1000 milliseconds from the following expiratory pause/inspirational phase). The difference between the longest and shortest interval is used as an index of RSA. Mean RSA in milliseconds was computed for every minute, by averaging the RSA values of all breaths falling within that minute.

Maximal exercise testing

Aerobic fitness of all subjects was operationalized as the maximum oxygen consumption during a supramaximal exercise test on a bicycle ergometer, according to Astrand & Rodahl.[621] A nine minute protocol was used, divided in three steps. Subjects started at a load of 50 Watts, pedaling at a constant speed of 60 rpm. After three minutes a second load of 100 to 140 Watts was imposed, the height of which was

dependent on the subjective assessment of maximal capacity by the experimenter (or, during second and third sessions, records from previous tests). The heart rate attained during the last minute of this second step was used to estimate the maximal oxygen consumption according to the nomogram of Astrand.[621] During the last three minutes of the test a load was imposed that required 20 % more oxygen consumption than the estimated maximum of the subject. This leads to a rapid maximalization of the aerobic energy yield. The remaining energy needed to sustain the supramaximal work load comes from anaerobic processes. Peak oxygen consumption measured during this supramaximal step is the subjects maximal oxygen consumption. The test was stopped once oxygen consumption did not rise any further, or if the subject gave up. During the test, the subject breathed through a high velocity, low resistance mouthpiece with minimal dead space that shunted all the expired air into a Maynhardt Ox-4 Oxycon. The Oxycon determined O_2 and CO_2 concentrations as well as total Ventilation per 30 second periods. From these, Carbon dioxide production (VCO_2) and oxygen consumption (VO_2) were determined. These volumes were converted to volumes in standardized conditions (0^oC; 760 mmHg; dry).

Maximal oxygen consumption is strongly related to body weight. However, aerobic endurance capacity is determined by the oxygen consumption in muscular tissue rather than fat tissue. Therefore, when comparing subjects, a correction is often made for differences in weight. In this study subjects were weighed before the start of the maximal test wearing only shorts. Absolute maximal oxygen consumption expressed in milliliters per minute was divided by body weight, yielding a weight corrected maximal oxygen consumption (Vo_{2max}).

Training

Between the first and the last laboratory session, 14 subjects participated in a program of endurance training. The program consisted of outdoor running and indoor fitness training. Subjects met four times a week for a training session of one hour and a half. All training sessions started with some warming up exercises for ten minutes. On two of the four days subjects ran a distance that was initially set to 4 km but was increased in the course of training to 15 km. The other two days were spent indoor, on a combination of conditioning exercises (three minute bouts of running, jumping in place, climbing up and down etc.), light weight training and aerobics. Exercises were chosen to train dynamic rather than static capacity and involved a large muscle mass. The combination of running and indoor exercises was chosen to prevent injury through selective overuse of a few muscles and tendons. All training sessions were kept at an intensity level of about 70% of subjects maximal capacity, by regularly checking the subjects pulse rates against their maximal HR. None of the subjects missed more than two of all scheduled training sessions.

Data quantification and analysis

The ECG, ICG and respiration signals were sampled continuously throughout the experiment, with the exception of the practice trials and the 15 minutes of relaxation between the cold pressor test and the post-stress period. From the post-stress resting period only the last five minutes were deemed of interest. During the two tasks, five blood pressure measurements were taken during minutes 2, 4, 6, 8 and 10. Recovery blood pressure was sampled in the first and third minutes of both recovery periods. Only one blood pressure measurement was taken during the cold pressor test, and it was started after 30 seconds of submersion. Post-stress blood pressure was measured during minutes 6, 8 and 10. An average value for all recorded minutes was available for HR and the $\Delta Z/\delta t$ derived measures as well as for the ventilation parameters. Since we were not interested in the within-condition variation, all measurements made during one condition were averaged to yield a single condition mean. For all physiological variables therefore, six average levels resulted, representing 1) ten minutes Memory Search task (MS), 2) five minutes of recovery from the memory search task (R1), 3) ten minutes Tone Avoidance task (TA), 4) five minutes of recovery from the tone avoidance task (R2), 5) one minute cold pressor test (CP) and 6) the five last minutes of the post-stress condition (POST). The post-stress condition rather than the pre-stress condition was used as a baseline. The rationale for discarding the pre-stress data was that there may be anticipatory reactions to the experimental conditions[342] , which have an as yet undefined relationship with aerobic fitness.

To outline the physiological response to the laboratory stressors, four sets of related variables were separately submitted to multivariate analyses of variance with the conditions as a repeated measurement factor. These sets comprised of 1) a blood pressure set (DBP, SBP and MAP) 2) a respiration set (TTI, TTE and TCT) 3) a cardiac set (PEP, RSA and HR) and 4) a resistance/output set (TPR, SV and CO). The 4V option of the BMDP statistical software package[125] was used for this purpose. Significant multivariate terms were followed by univariate F-tests to determine the effects of the laboratory conditions on individual variables. Since condition was entered as a repeated measures effect, corrected epsilon estimation was used according to the Greenhouse Geisser correction procedure as recommended by Vasey & Thayer.[590] Degrees of freedom reported are the values given by BMDP, rounded to the nearest integer. Where univariate analyses revealed a significant main effect, post-hoc analysis was carried out using the Newman Keuls procedure[614] , that compares the difference of condition means to a criterion based on the studentized range statistic ($p's < 0.05$). The interindividual reliability of the absolute value of impedance cardiography derived stroke volume is still a matter of controversy .[462] Since this study was primarily concerned with reactivity, we did not aim at more than intra-individual reliability of SV, CO and TPR. Therefore, the response of these variables to the various conditions was expressed as a percentual change from post-stress level, and the post-stress level was excluded from the analyses.

The cross-sectional relationship between fitness and reactivity was assessed using correlational analysis on the data collected during the first session (pre-training). First, reactivity (recovery) scores were computed as the difference between task (recovery)

means and the mean post-stress level (percentual changes relative to the post-stress levels were used for SV, CO, and TPR). Next, Pearson product moment correlation coefficients (BMDP8D) were computed between Vo_{2max} and the reactivity (recovery) scores of all variables.

Data analysis of training effects was performed by group(2)Xsession(3) repeated measures MANOVAs on the reactivity (recovery) scores for all task (recovery) periods separately. Significant multivariate terms were followed by univariate F-tests to determine the experimental effects on individual variables.

Results

Physiological reactivity to the laboratory stressors

Figure 2 displays the physiological response to all conditions during the first laboratory session in the pre-training phase of the experiment. Panel a shows the mean levels of arterial, systolic and diastolic blood pressure during all six conditions. These blood pressure levels were submitted to a MANOVA that yielded a highly significant effect of condition ($F(15,312)=12.75$, $p<0.0001$). Follow up analysis showed a significant univariate effect for all three blood pressure parameters individually ($F_{MAP}(3,64)=25.51$, $p<0.0001$; $F_{DBP}(3,63)=42.49$, $p<0.0001$; $F_{SBP}(4,88)=36.10$, $p<0.0001$). Post-hoc comparison of the condition means of the MAP showed that resting and recovery levels were not different from each other but significantly different from the task levels($p's<0.05$). All three tasks evoked a significant increase in MAP over the post stress resting level, that varied from 11 mmHg during the memory search task to 13 mmHg during the tone avoidance task and 15 mmHg during the cold pressor test. These task levels were not significantly different from each other. This pattern of blood pressure reactivity was essentially repeated by both the DBP and the SBP, which went up in response to all three tasks, but were quickly restored to resting level during the recovery periods. In addition, SBP was significantly lower during the cold pressor test (M = 130.4) than during the memory search task (M = 134.4). During the tone avoidance task SBP fell in between these values (M = 132.9) but was not significantly different from either task.

Panel b of Figure 2 shows the respiratory time intervals during all conditions. The multivariate effect of condition on this set was clearly significant ($F(15,312)=22.70$, $p<0.0001$). Univariate analysis showed all three respiratory intervals to change significantly over conditions ($F_{TCT}(4,81)=32.11$, $p<0.0001$; $F_{TTI}(4,84)=27.9$, $p<0.0001$) ; $F_{TTE}(4,85)=37.05$, $p<0.0001$). During both reaction time tasks, total cycle time decreased significantly below the resting level. Expressed as an increase in respiration rate, this means that RR rose from a mean value of 14 cpm in the resting condition to 19 cpm during the memory search task. During the tone avoidance task RR rose to 18 cpm. After the tasks RR returned rapidly to the resting level. In contrast to the reaction time tasks there was no change in RR during the cold pressor test.

The increase in RR during the reaction time tasks could be attributed to decreases of both inspiration and expiration. Total time inspiration and total time expiration during both tasks decreased significantly below levels attained during the resting and recovery

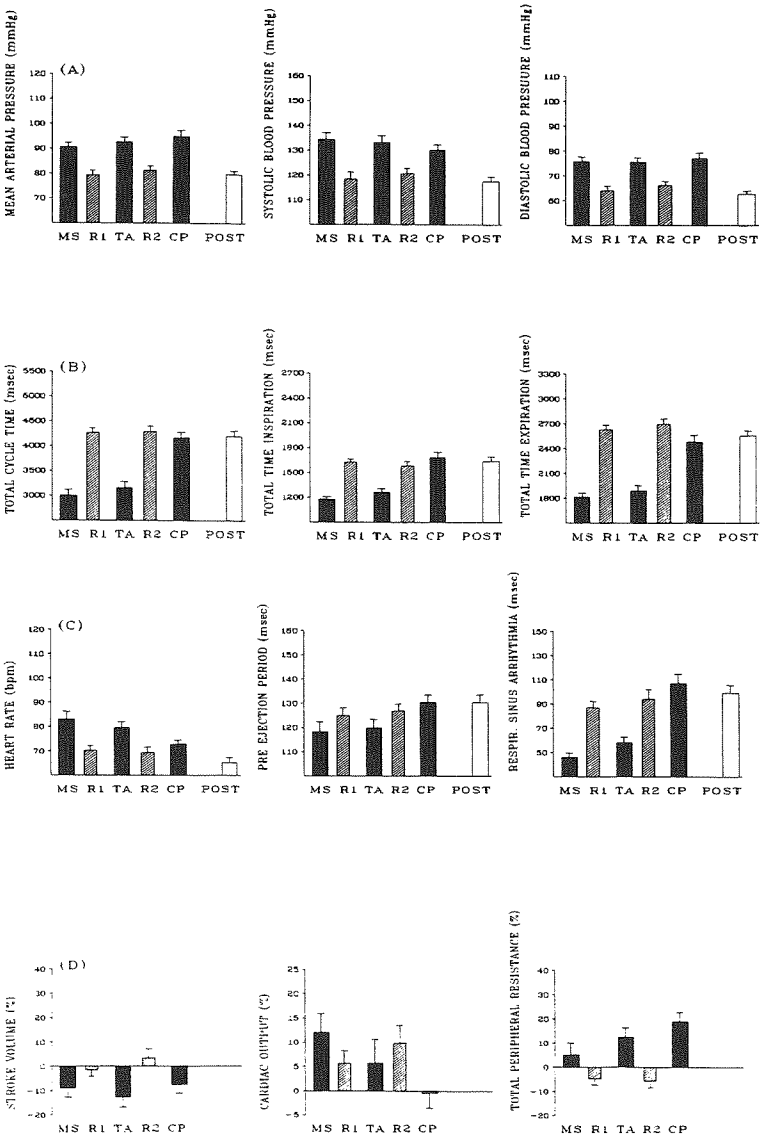

Figure 2: Levels of the physiological variables during the first session (N=24). Presented are the mean values (±1 standard error) during the Memory Search task (MS), recovery from this task (R1), the Tone Avoidance task (TA), recovery from this task (R2), the Cold Pressor test (CP) and a post-stress resting condition (POST). In *panel d* the mean percentual change from the post-stress level is given for the stroke volume, cardiac output and the total peripheral resistance.

conditions, or the CP test. Total time inspiration time decreased from resting level by 23 % during the memory search task and by 22 % during the TA task. Decreases in TTE were 25 % and 26 % respectively. The increase in RR during these tasks therefore, seemed to be caused by a proportionally equal shortening of in- and expiration phases.

MANOVA on the set of cardiac variables also resulted in a significant multivariate effect of condition ($F(15,312)=14.56$, $p<0.0001$). Follow up univariate analyses showed that heart rate clearly differed between conditions ($F(3,58)=33.18$, $p<0.001$). HR during recovery (M_{R1} = 70.2, M_{R2} = 69.3) was significantly higher than the resting HR (M = 65.3). During all three tasks HR was significantly higher than either the resting HR or HR during the recovery conditions. Furthermore, there was a difference in HR-reactivity among the tasks themselves. HR level was highest during the memory search task (M = 83.0) and lowest during the cold pressor (M = 72.8), with HR response to the TA task falling in between (M = 79.5).

Apart from the chronotropic response to the reaction time tasks, there appeared to be a strong inotropic response as well, evidenced by the significant univariate condition effect on the PEP ($F(3,72)=15.27$, $p<0.001$). During the two reaction time tasks the PEP (M_{MS} = 118.2; M_{TA} = 119.9) was significantly lower than during the resting condition (M = 130.5), pointing to an increase in β-adrenergic drive on the heart. In contrast, the PEP remained essentially unchanged during the cold pressor test. During recovery from the tone avoidance task, PEP (M = 130.5) returned to a level not different from the resting level. During recovery from the memory search task however, PEP (M = 124.9) remained lower than the PEP measured post-stress, although the recovery relative to the preceding task level was significant. Obviously some restoration of normal inotropic drive had occurred after 5 minutes, but, as with the HR, recovery to the resting level was as yet not complete.

Respiratory sinus arrhythmia clearly changed as a function of condition ($F(3,74)=18.69$, $p<0.0001$). Post-hoc analyses showed that RSA during the two reaction time tasks (M_{MS} = 45; M_{TA}=56) was significantly lower than during the resting condition (M = 99). The response to the MS task seemed somewhat stronger than the response to the tone avoidance task, but the difference was not significant. The decrease in RSA during the reaction time tasks points to a reduction of vagal inhibitory effects on the SA node. Recovery levels of RSA were not different from the resting level, suggesting rapid restoration of vagal influences after termination of the stressors. During the cold pressor test, RSA did not change significantly from the resting level. Apart from changes in central vagal tone, cardiac vagal effects may depend on changes in the ventilatory pattern.[220] Since RR clearly went up during the tasks in this experiment, this might have explained the decrease in RSA. However, Pearson product moment correlation coefficients between changes in RR and RSA were not significant. This suggests that the change in RSA was mainly an effect of a change in the central control of vagal activity.

Panel d of Figure 2 shows the percentual changes in stroke volume, cardiac output and total peripheral resistance from the post stress resting level. MANOVA on the effect of condition on these changes yielded a highly significant F-value ($F(12,238)=10.43$, $p<0.0001$). Univariate analyses on SV ($F(3,72)=6.25$, $p<0.0007$), CO ($F(3,82)=2.56$, $p<0.05$) and TPR ($F(3,72)=8.58$, $p<0.0001$) all yielded significant condition effects. In

spite of the increased inotropic drive (PEP), SV decreased during all conditions, except during recovery from the tone avoidance task. Post-hoc comparison of the SV changes during all conditions showed that the SV responses to recovery were different from the responses to the tasks. The decrease in SV during either the memory search task (-9.9%), the tone avoidance task (-10.8%), or the cold pressor test (-7.5%) was larger than the decrease in SV during recovery from the memory search task (-1.6%). SV even increased slightly during recovery from the tone avoidance task (+3.4%), and this response was significantly different from the response to all other conditions. The SV response pattern can be summarized as a decrease during the tasks followed by a restoration to resting levels during recovery.

In spite of the general decrease in SV, CO increased above the resting level during all conditions except the cold pressor test. Clearly the increase in HR was large enough to raise total minute output, even in the face of a reduced SV. Post-hoc comparison of mean CO changes during all conditions showed that increases in CO during the MS task (M = 12.0%) and the recovery from the tone avoidance task (M = 9.9%) were significantly different from the CO response to the cold pressor(M = -0.5%). The increases in CO during the TA task (M = 6.7%) and during recovery from the MS task (M = 5.6%) fell in between, and were not significantly different from any of the other conditions.

These results suggested that CO increased above the resting value during most conditions, notably the memory search task. However, no direct comparisons of task levels with the post-stress resting level were made, since we had used percentual differences from the post-stress level, and omitted the post stress condition in the analyses. Thus, it remained to be established whether CO really increased during these conditions. Therefore, it was tested whether the changes in CO were significantly different from zero (BMDP delivers this test automatically). CO appeared to increase significantly above resting values during the memory search task ($F(1,23)=6.72$, $p<0.01$) and the tone avoidance task ($F(1,23)=5.97$, $p<0.02$), and remained elevated during the 5 minute recovery periods after the tasks ($F_{R1}(1,23)=5.53$, $p<0.03$; $F_{R2}(1,23)=11.90$, $p<0.002$). During the cold pressor test, the change in CO from the resting level was not significant.

Total peripheral resistance increased during all three tasks but decreased again during the two recovery periods. Post-hoc contrasts showed that the increase during the cold pressor test (18.8%) was higher than the increase during the tone avoidance task (12.4%) and that the latter again was higher than the increase during the MS task (5.1%). The decreases in TPR during recovery were significantly different from the responses to all three tasks, but were not different among themselves (M_{R1} = -4.7% ; M_{R2} = -5.6%). To assess whether the changes in TPR from the resting level during any of the conditions were significant, the TPR changes were tested against the hypothesis of no change, parallel to the procedure followed for the CO. This showed that TPR increased during the TA task ($F(1,23)=5.85$, $p<0.03$) and the cold pressor test ($F(1,23)=11.27$, $p<0.005$) but did not change significantly during the memory search task. After the tasks TPR fell below the post-stress level, but the decreases below this resting value were not significant.

Before investigating the relationship between physiological reactivity and aerobic fitness, we will summarize the physiological response to the experimental conditions: All three tasks evoked strong cardiac and blood pressure reactions with substantial

increases in both HR and MAP. Most of these reactions had disappeared within 5 minutes of recovery, with the exception of the β-adrenergic drive on the heart as evidenced by the elevated HR and CO, and the shorter PEP. This suggests that neurogenic activity ceases rapidly once the tasks are ended, whereas hormonal effects of adrenaline on the cardiac receptors remain present. The marked fall in TPR after the tasks is compatible with this view, since this is likely to be caused by the vasodilatory effects of adrenaline in the muscles, that are no longer opposed by neurogenic vasoconstriction. Apart from sympathetic effects, cardiovascular reactivity to the reaction time tasks seemed to be influenced by changes in vagal tone, as evidenced by the change in RSA. These changes could not be fully explained by changes in RR, although RR was seen to go up substantially during these tasks. The increase in MAP was mainly brought about by an increased CO during the memory search task, by an increase in both CO and TPR during the tone avoidance task and an increase in TPR during the cold pressor test. The clear differences in resistance and output changes during the three tasks confirmed our expectations that these tasks would evoke different cardiovascular response patterns.

Pre-existing differences in aerobic fitness

Resting levels

Maximal oxygen consumption values measured during the supramaximal exercise test in the pre-training session showed considerable interindividual shatter. In the 24 subjects, it ranged from 2.3 to 4.3 liters, which after correction for weight amounted to a range of 33.2 to 54.9 ml. The mean Vo_{2max} was 46.4 ml with a standard deviation of 5.1 ml. Vo_{2max} was not related to age or height. These values correspond well with those reported by others who have measured aerobic fitness in a similar young male sedentary population.[621]

To assess the relation of these pre-existing differences in fitness with physiological and psychological characteristics, Pearson product moment correlation coefficients were computed between the post-stress levels of the physiological variables, anxiety scores and Vo_{2max}. SV derived variables were left out of these analyses. Vo_{2max} was negatively correlated with DBP($r = -0.33$, $p=0.10$), SBP($r = -0.29$, $p=0.13$) and HR($r = -0.30$, $p=0.12$). Although these relations were not significant, all p-values were smaller than 0.15, suggesting that a larger sample would have resulted in a significant relation. There was no relation between PEP, RSA or RR at rest and Vo_{2max}, although resting sinus arrhythmia showed the expected relationship to HR($r = -0.57$, $p<0.002$) and RR($r = -0.40$, $p<0.05$). State nor trait anxiety were correlated with post-stress levels of any of the physiological variables. Furthermore, there was no relation between state or trait anxiety and Vo_{2max}.

Physiological reactivity

Table 2 shows the relationship between stress-reactivity and Vo_{2max}. During the memory search task only one significant relation was found. The decrease in RSA was smaller in the more fit subjects($r = 0.40$, $p<0.05$). This suggests that vagal inhibitory

influences on the myocardium remained more intact in the more fit subjects.

Table 2: Pearson product moment correlation coefficients between weight-corrected maximal oxygen consumption and physiological reactivity (N = 24). Reactivity (recovery) of the physiological variables was defined as the change from the post-stress resting level.

	Memory Search task	Recovery from the MS task	Tone Avoidance task	Recovery from the TA task	Cold Pressor
DBP	-0.37	-0.26	-0.50**	-0.30	-0.04
SBP	-0.01	-0.15	-0.18	0.04	-0.18
MAP	-0.32	-0.21	-0.40*	-0.13	-0.02
TTI	0.10	0.09	0.07	-0.13	0.07
TTE	-0.06	-0.16	0.08	-0.20	0.03
RR	-0.00	0.03	0.00	0.17	-0.05
RSA	0.40*	0.13	0.41*	0.24	0.09
PEP	-0.16	-0.07	-0.10	-0.02	-0.04
HR	-0.11	0.06	-0.16	-0.06	-0.12
CO	0.05	-0.09	0.18	-0.29	-0.14
SV	0.14	-0.10	0.24	-0.21	-0.09
TPR	-0.19	-0.02	-0.35	0.22	0.19

*) $\alpha < 0.05$, **) $\alpha < 0.01$

Mean arterial (r = -0.32, p=0.11) and diastolic (r = -0.37, p=0.07) blood pressure reactions tended to be smaller in the more fit subjects, but the relations did not reach significance. Changes in the CO, PEP or HR during the memory search task were not related to fitness. There was no relation between fitness and the RR response either, suggesting that the smaller RSA responses in fit subjects were not mediated by the ventilatory response.

The smaller vagal withdrawal (RSA) in the more fit subjects was replicated during the tone avoidance task (r = 0.41, p<0.04). At the same time, the more fit subjects had significantly smaller increases in mean arterial (r = -0.40, p<0.05) and diastolic (r = -0.50, p<0.01) blood pressure. Since increases in the TPR played an important role in blood pressure reactivity to this task, we expected the lower blood pressure response of the more fit subjects to coincide with a reduced increase in TPR. High Vo_{2max} values were indeed associated with a reduced TPR response but the correlation was only marginally significant (r = -0.35, p=0.09). During the tone avoidance task there was again no relation between fitness and the CO, PEP or HR responses. No significant relationship at all existed between Vo_{2max} and reactivity of any of the variables during the cold pressor test. Furthermore, there was no association between fitness and the recovery levels after the two reaction time tasks.

Task levels

Since a high Vo_{2max} tended to be associated with lower levels of resting blood pressure as well as with lower reactivity to the tasks, we decided to look at the relationship

between Vo_{2max} scores and absolute blood pressure levels attained during stress. During the memory search task, diastolic, mean arterial and systolic blood pressure levels were clearly lower in the more fit subjects with correlation coefficients of -0.47, -0.48 and -0.41 respectively (p's<0.03). These relatively low blood pressure levels in the more fit subjects were replicated during the TA task (r_{DBP} = -0.51, r_{MAP} = -0.51, r_{SBP} = -0.46 p's<0.02). Interestingly, the absolute HR attained during the MS (r = -0.38, p=0.05) and tone avoidance (r = -0.49, p<0.02) tasks were also inversely related to the Vo_{2max} scores, although the relation between fitness and resting HR nor HR-reactivity did reach significance. No relation between fitness and task levels of any of the other variables was seen.

Performance measures

The relationship of aerobic fitness with DBP and RSA reactivity might have been caused by differences in task performance. Pearson product moment correlations between the number of correct responses and physiological reactivity to both reaction time tasks showed no significant effects. However, the mean reaction time during the trials of the memory search task was significantly related to several physiological responses. PEP- (r = 0.40, p<0.05), CO- (r = -0.42, p<0.05) and HR-reactivity (r = -0.61, p<0.01) were all related to the mean reaction time, in a manner suggesting that the fastest responders had the highest β-adrenergic cardiac drive during this task. This may reflect a coupling between cognitive effort invested in the task and adrenergic responses, but it may also reflect differences in subjective emotional arousal. No data were collected to test these alternatives. More importantly however, it could be shown that none of the performance measures in either task were related to aerobic fitness.

In summary, analysis of the data on the first session have shown that the RSA- and DBP-reactivity to active coping tasks is lower in the more fit subjects. Absolute HR and BP levels during the tasks were also lower in the more fit subjects. These effects were independent of the differences in anxiety or task performance. There was no relation between fitness and the recovery from the tasks, nor between fitness and the response to the cold pressor test.

Training

Table 3 presents several characteristics of the subjects in the training and waiting list control group that were measured before, three and a half weeks into, and after training. To test for initial group differences a one-way ANOVA was performed on Vo_{2max}, height, weight, anxiety measures and the resting levels of the physiological variables before training. This showed that the groups differed only in resting SBP ($F(1,20 = 3.9$, $p<0.05$), that was lower in the control group. HR tended to be lower in the training group, but the effect was not significant ($F(1,20)=3.12$, $p<0.1$). Vo_{2max}, weight and height did not differ between the groups, nor did trait or state anxiety. Given the amount of variables this shows that randomization had been fairly successful.

To assess the effects of training on aerobic fitness, analysis of variance was conducted on the Vo_{2max} of both groups during all three sessions. There was a significant

Table 3: Post stress resting levels (±1 standard error) of the physiological variables measured during the pre-training laboratory session (I), a second session three and a half weeks into training (II) and the last session after the completion of the training period (III). Lower half shows height (cm) and trait/state anxiety scores in both groups at the first session, and the absolute (l/kg.min) and weight corrected maximal oxygen consumption (ml/kg.min) during the maximal exercise tests.

	TRAINING			CONTROL		
	I	II	III	I	II	III
DBP (mmHg)	64.6 (5.8)	64.6 (6.0)	66.3 (5.8)	60.9 (8.0)	66.8 (7.0)	67.5 (9.0)
SBP (mmHg)	120.8 (8.4)	120.4 (7.5)	120.5 (8.1)	112.8 (10.5)	115.8 (7.8)	115.2 (8.9)
MAP (mmHg)	81.1 (6.2)	79.6 (5.2)	79.8 (4.8)	78.9 (7.1)	80.9 (6.6)	82.5 (7.9)
RSA (msec)	102 (38)	107 (38)	92 (40)	99 (56)	98 (47)	107 (54
PEP (msec)	127 (16)	126 (13)	131 (19)	134 (16)	136 (15)	132 (7)
HR (bpm)	62.8 (6.4)	57.5 (6.8)	58.3 (5.8)	70.3 (14.7)	62.5 (11.6)	63.5 (13.5)
RR (cpm)	14.2 (2.0)	15.3 (2.1)	16.1 (1.9)	14.0 (1.9)	13.7 (2.0)	14.1 (2.1)
HEIGHT (cm)	182.7 (3.1)			187.0 (5.2)		
TRAIT anxiety	32.7 (5.8)			31.3 (3.6)		
STATE anxiety	33.0 (6.6)	30.1 (4.4)	30.7 (7.1)	33.6 (6.9)	33.3 (4.5)	32.0 (6.7)
WEIGHT (kg)	76.5 (7.3)	76.4 (7.5)	76.1 (7.5)	71.7 (10.3)	71.4 (10.8)	71.4 (10.5)
Vo_2max (l/min)	3.55(0.4)	3.83(0.5)	3.87(0.5)	3.44(0.6)	3.35(0.4)	3.32(0.4)
Vo_2max/kg (ml/min/kg)	46.6 (5.6)	50.3 (5.7)	51.9 (5.6)	47.8 (4.9)	47.3 (5.2)	46.7 (5.8)

groupXsession interaction ($F(2,36)=10.38$, $p<0.004$). Vo_2max of the trained subjects increased by 5.2 ml, that amounted to a relative increase of 11 %. Given the duration of training, this is about the effect that could be expected from similar training studies.[523, 564] Vo_2max of the control group remained unchanged. ANOVA on weight and state anxiety scores showed no session or sessionXgroup interaction effects.

From the univariate group(2) X session(3) ANOVAs on the resting levels of the physiological variables, significant interactions emerged only for DBP ($F(2,36)=4.87$, $p<0.02$) and RR ($F(2,30)=3.60$, $p< 0.05$). From table 3 it can be seen that this effect is due to the unexpectedly low DBP of the control group in the first session. Respiration rate of the trained subjects changed in the course of training, whereas it remained constant in the control group. In table 3 it can be seen that training led to an increase in resting RR. ANOVA on the resting levels of MAP, SBP, HR, RSA and PEP showed no other groupXsession interactions. However, HR did change over sessions. In the first session the resting HR in both groups was elevated compared to session II and III, yielding a significant main effect of session ($F(2,39)=13.35$, $p<0.0001$).

Physiological reactivity

Table 4a shows the task-induced reactivity of all variables in all three sessions. A quick glance at this table suggests that there is no effect of endurance training on the reactivity of any of the variables during any of the conditions. Analysis of variance by and large confirmed the absence of this effect, since there were virtually no significant groupXsession interactions. The only exception was a significant multivariate

Table 4a: Physiological reactivity (±1 standard error) to the Memory Search task (MS), the Tone Avoidance task (TA) and the Cold Pressor test (CP). Reactivity to these tasks was measured during the pre-training laboratory session (I), a second session three and a half weeks into training (II) and a third session after the completion of the training period (III). Reactivity scores are given separately for the group receiving training (left) and the waiting list control group (right).

	TRAINING			CONTROL		
	I	II	III	I	II	III
	Memory Search Task (MS)					
DBP (mmHg)	12.8 (1.7)	9.9 (2.0)	8.8 (2.0)	12.7 (2.6)	12.3 (3.1)	9.2 (2.8)
SBP (mmHg)	17.0 (2.9)	13.7 (2.6)	13.7 (2.6)	15.1 (3.7)	17.7 (5.2)	12.8 (4.7)
MAP (mmHg)	10.6 (1.9)	9.5 (2.4)	11.0 (1.9)	9.6 (2.6)	14.2 (4.1)	10.8 (2.9)
RR (cpm)	6.3 (0.8)	6.0 (0.7)	4.0 (1.2)	4.9 (0.8)	5.7 (0.7)	6.9 (1.0)
RSA (msec)	-60.0 (8.7)	-59.0 (8.0)	-47.0 (8.9)	-33.0 (6.0)	-56.0 (11.7)	-42.0 (7.0)
PEP (msec)	-9.4 (2.6)	-13.5 (3.2)	-9.9 (3.0)	-15.7 (5.4)	-16.6 (4.6)	-14.4 (4.8)
HR (bpm)	17.9 (2.9)	18.4 (1.9)	16.3 (2.5)	17.9 (5.6)	24.2 (4.6)	18.4 (3.6)
SV (%)	-12.3 (4.4)	-5.6 (4.9)	-4.3 (3.4)	-5.0 (6.8)	-4.9 (6.5)	0.5 (7.4)
CO (%)	12.7 (5.8)	19.3 (5.2)	11.4 (6.0)	16.4 (9.3)	22.1 (8.5)	21.0 (8.7)
TPR (%)	6.4 (6.5)	-3.7 (5.3)	9.5 (11.5)	-0.7 (6.1)	-5.1 (6.6)	-2.4 (7.6)
	Tone Avoidance Task (TA)					
DBP (mmHg)	12.9 (1.8)	12.5 (2.4)	8.9 (1.6)	14.3 (1.2)	11.6 (3.3)	8.4 (2.9)
SBP (mmHg)	16.9 (2.6)	14.1 (3.6)	12.9 (2.5)	14.8 (2.8)	16.7 (3.9)	11.1 (3.8)
MAP (mmHg)	14.3 (2.2)	13.2 (2.7)	11.5 (1.8)	11.4 (1.6)	11.9 (4.0)	8.9 (2.8)
RR (cpm)	3.4 (0.5)	3.1 (1.0)	5.0 (0.6)	3.9 (1.2)	5.1 (0.9)	3.9 (0.6)
RSA (msec)	-49.0 (7.7)	-48.0 (8.0)	-29.0 (9.4)	-18.0 (8.1)	-30.0 (10.2)	-15.0 (10.4)
PEP (msec)	-7.8 (2.6)	-9.6 (2.5)	-8.0 (3.1)	-15.0 (3.5)	-16.8 (5.1)	-14.6 (3.8)
HR (bpm)	14.8 (2.4)	15.0 (1.8)	12.8 (1.7)	13.9 (2.9)	17.2 (3.9)	16.5 (2.4)
SV (%)	13.0 (3.9)	-8.0 (4.4)	-14.0 (3.8)	-3.7 (6.1)	-4.1 (6.6)	-6.8 (5.9)
CO (%)	6.4 (4.5)	11.3 (4.4)	2.8 (4.0)	10.8 (7.6)	15.0 (9.3)	7.7 (4.1)
TPR (%)	15.6 (5.8)	7.3 (6.0)	14.5 (6.4)	-0.2 (7.8)	3.8 (6.7)	5.2 (5.7)
	Cold Pressor Test (CP)					
DBP (mmHg)	15.4 (2.6)	14.3 (2.9)	16.8 (2.7)	13.8 (3.2)	12.9 (3.2)	12.6 (3.6)
SBP (mmHg)	13.7 (2.2)	11.4 (2.4)	15.6 (2.7)	11.9 (3.0)	9.6 (3.7)	9.9 (4.1)
MAP (mmHg)	13.6 (2.7)	14.5 (2.9)	21.6 (5.1)	11.0 (3.4)	13.8 (3.7)	11.1 (4.3)
RR (cpm)	-1.2 (0.8)	0.3 (1.4)	0.5 (0.6)	-0.6 (0.9)	-1.2 (0.7)	0.9 (1.3)
RSA (msec)	11.5 (10.4)	19.0 (15.3)	32.0 (15.5)	2.0 (9.3)	-2.0 (5.9)	-4.0 (10.8)
PEP (msec)	2.5 (2.5)	1.0 (1.1)	2.1 (1.8)	-4.6 (1.9)	-5.0 (3.4)	-3.8 (2.1)
HR (bpm)	8.2 (1.2)	6.9 (1.9)	5.0 (1.8)	6.9 (2.9)	11.4 (2.9)	10.3 (3.1)
SV (%)	-11.9 (2.3)	-8.6 (4.0)	-9.9 (2.3)	-1.2 (7.3)	-5.9 (4.9)	-7.7 (6.9)
CO (%)	-4.6 (2.7)	0.2 (3.8)	-1.9 (1.6)	0.7 (7.5)	2.9 (4.5)	0.7 (6.1)
TPR (%)	23.5 (4.6)	20.4 (6.0)	29.7 (4.4)	16.5 (6.9)	19.5 (6.2)	18.2 (9.3)

groupXsession interaction effect ($F(6,76)=2.31$, $p<0.05$) on the blood pressure set during the cold pressor test. Univariate follow up analysis of this effect showed a marginally significant groupXsession interaction in the MAP response ($F(2,39)=2.35$, $p< 0.1$). Since no such effect was seen in either DBP or SBP, and three and a half weeks of training did not cause a change in MAP response, it is doubtful whether the interaction is meaningful. In none of the other sets of variables a significant multivariate interaction between training and session could be found during the reaction time tasks, the cold pressor test, or the two recovery periods after the tasks. From these analyses it may be concluded therefore, that training did not influence the physiological stress response.

Possibly, the absence of a training effect was due to habituation. Reactivity during the second and third sessions might have been reduced to a level were group differences could not be detected. From the group(2) X session(3) MANOVAs on the blood pressure responses to the memory search and tone avoidance tasks significant main effects of session emerged ($F_{MS}(6,76)=2.20$, $p<0.05$; $F_{TA}(6,76)=2.49$, $p<0.03$). Since blood pressure reactivity to these tasks generally decreased over sessions, the multivariate session effect may indeed reflect habituation. However, follow up univariate analysis showed only a significant change in DBP response over sessions during the tone avoidance task ($F(2,38)=4.64$, $p<0.02$). From table 4a it can be gathered that DBP-reactivity to the TA task decreased over time, but that the DBP responses at session three were nevertheless substantial. The respiratory pattern seen during the first session was repeated almost exactly during the second and third sessions. The same was true for the cardiac and output (resistance) sets. No significant multivariate effects of session on the reactivity of any of these variables emerged during the reaction time tasks or the cold pressor test.

Table 4b: Recovery from the Memory Search task (R1) and from the Tone Avoidance task (R2) expressed as changes from the post-stress resting level (±1 standard error). Recovery from these tasks was measured during the pre-training laboratory session (I), a second session three and a half weeks into training (II) and a third session after the completion of the training period (III). Recovery scores are given separately for the group receiving training (left) and the waiting list control group (right).

	TRAINING			CONTROL		
	I	II	III	I	II	III
	Recovery from the MS task (R1)					
DBP (mmHg)	0.9 (0.9)	0.5 (1.2)	-0.8 (1.3)	2.6 (2.1)	1.3 (1.9)	0.2 (1.5)
SBP (mmHg)	2.5 (2.1)	6.0 (2.3)	3.0 (1.4)	0.1 (2.0)	7.9 (3.7)	3.7 (3.3)
MAP (mmHg)	0.5 (1.6)	1.6 (1.5)	1.4 (1.6)	0.1 (2.4)	3.7 (2.2)	1.3 (1.6)
RR (cpm)	-1.4 (0.4)	-1.4 (0.8)	-0.2 (0.4)	0.2 (0.5)	0.2 (0.4)	0.6 (0.5)
RSA (msec)	-2.0 (6.9)	-17.0 (5.7)	3.0 (12.1)	-19.0 (10.9)	7.0 (10.1)	-3.0 (10.9)
PEP (msec)	-5.3 (1.7)	-11.0 (1.7)	-5.4 (1.9)	-6.8 (2.8)	-12.6 (3.7)	-10.4 (2.8)
HR (bpm)	4.8 (1.2)	4.4 (0.5)	4.8 (0.8)	6.1 (1.4)	8.2 (1.5)	10.4 (1.4)
SV (%)	-1.6 (2.8)	0.2 (2.8)	-2.4 (2.4)	-0.7 (4.7)	1.7 (4.8)	6.2 (5.3)
CO (%)	5.7 (3.2)	12.5 (3.0)	6.5 (1.7)	7.7 (5.1)	14.6 (4.7)	10.0 (5.2)
TPR (%)	-3.5 (2.9)	-8.0 (6.0)	-3.6 (3.2)	-9.5 (3.9)	-7.8 (6.7)	-4.6 (4.3)
	Recovery from the TA task (R2)					
DBP (mmHg)	3.9 (1.1)	1.5 (1.2)	0.2 (0.8)	2.9 (1.1)	1.9 (1.8)	0.6 (1.4)
SBP (mmHg)	2.9 (1.7)	5.8 (2.3)	4.2 (1.6)	2.9 (1.7)	4.3 (2.0)	2.5 (2.9)
MAP (mmHg)	1.1 (1.1)	3.7 (2.0)	0.8 (1.9)	1.8 (2.0)	2.9 (1.5)	1.0 (1.5)
RR (cpm)	-0.6 (0.5)	-1.4 (0.9)	-0.1 (0.4)	-0.3 (0.8)	-0.3 (0.3)	0.7 (0.6)
RSA (msec)	-3.0 (6.8)	-15.0 (4.7)	-3.0 (6.0)	4.0 (8.9)	-6.0 (10.7)	-7.0 (7.9)
PEP (msec)	-2.7 (2.9)	-8.5 (2.0)	-8.8 (3.3)	-5.6 (2.3)	-10.0 (3.3)	-12.5 (2.3)
HR (bpm)	3.6 (3.5)	4.3 (1.3)	3.9 (1.4)	4.8 (1.5)	6.9 (1.5)	6.1 (0.9)
SV (%)	3.1 (3.9)	4.7 (2.9)	-0.4 (2.6)	5.7 (4.4)	4.3 (5.6)	0.5 (6.2)
CO (%)	10.0 (4.2)	11.8 (2.4)	6.2 (3.0)	7.6 (4.5)	10.7 (4.6)	6.4 (6.5)
TPR (%)	-5.9 (4.1)	-5.6 (2.9)	-3.9 (3.4)	-3.3 (4.3)	-4.4 (3.8)	-4.3 (4.9)

Table 4b shows the response to the recovery periods following each of the reaction time tasks in all three sessions. Recovery from the stressors was generally not different on retesting after three and a half or seven weeks. However, in the cardiac set significant multivariate effects of session did emerge for recovery from both the memory search,

(F(6,76)=2.24, p<0.05) and tone avoidance tasks (F(6,76)=2.36, p<0.04). Univariate analysis showed that the recovery of PEP after the memory search (F(2,37)=4.51, p<0.03) and the tone avoidance tasks (F(2,32)=3.34, p<0.05) changed over sessions. Recovery of the PEP after these tasks was even less complete during session two and three than it had been during session one. This effect was present in both groups and may reflect the fact that the anticipatory response to the next stressor gets stronger after a first confrontation with the stressors. Since no groupXsession interaction on the recovery levels had emerged, training appeared to have no reducing or enhancing influence on this anticipation. Taken together, the results of the analyses of session main effects do not suggest that habituation to the stressors prevented the demonstration of a training effect on task reactivity or recovery.

Although effects of habituation (session) and training (groupXsession) were largely lacking, significant multivariate effects of group suggested that, in all sessions, cardiac reactivity of the control group differed from that of the training group. Univariate follow-up analyses showed that a significant group difference existed for the PEP ($F_{TA}(1,20)=4.14$, $p<0.03$, $F_{CP}(1,20)=11.19$, $p<0.004$), CO ($F_{TA}(1,20)=3.89$, $p<0.05$, $F_{MS}(1,20) = 4.01$, $p<0.05$) and TPR responses ($F_{TA}(1,20)=3.61$, $p<0.05$, $F_{MS}(1,20)=10.81$, $p<0.005$). In response to the cold pressor and the tone avoidance task, PEP decreased more in the control group subjects than in the training group subjects. Throughout all sessions, the control group responded with a higher CO increase and a lower TPR decrease to the reaction time tasks than the training group. This may reflect a stronger β-adrenergic response to active coping tasks in the control group. These group differences in β-adrenergic drive were already present at the first session and were not influenced by training.

The high cardiac drive in the control group may reflect better performance since we previously showed a relation between the mean reaction time and PEP-, HR-, and CO-reactivity. Reaction time during both tasks appeared to decrease clearly over sessions ($F(2,36)=41.58$, $p< 0.0001$; $F_{TA}(2,32) = 10.81$, $p<0.0004$). Together with an increase in the percentage correct responses ($F_{MS}(2.30 = 41.90$, $p<0.0001$; $F_{TA}(2,30)=29.05$, $p<0.0001$) this suggested an overall increase in performance from session I to session III. However, there were no interaction effects of session with group membership, showing that both groups improved their performance equally. Points gained during both tasks were summed into one score. This score represents each subjects total performance. The ANOVA on the ranking of the subject within the whole group based on these scores again showed no session or interaction effects, but a clear group effect did emerge ($F(1,20)=3.91$, $p<0.05$). The group effect reflected the fact that control subjects on the average performed somewhat better than the trained subjects. The higher performance of the control group may reflect some inherent group difference in performance-ability, but the generally higher CO and PEP responses in the control group would suggest a difference in effort expenditure. Since these differences were present at session one and did not change over sessions, it is difficult to imagine how they could change the conclusion that training did not influence the physiological reactivity to the tasks.

In summary our data do not support the idea that a short training program reduces stress-reactivity. Based on our cross-sectional results it seemed reasonable to expect such

a results at least for DBP- or RSA-reactivity, since these had been related to differences in Vo_{2max}. Had the manipulation of fitness been unsuccessful? As shown before, mean Vo_{2max} of the subjects in the training group went up significantly in the course of training. However, close inspection of the individual data revealed a strong interindividual difference in the response to training. The increase in the absolute values for maximal oxygen consumption in the trained group ranged from -0.57 to +0.84 ml with a mean value of 0.32 (sd = 0.33). The maximal oxygen consumption of two subjects even decreased, but since they lost weight, maximal oxygen consumption per kg body weight did still increase. After weight correction the group showed an average gain in fitness of 5.2 (±3.0) with a striking range of 1.7 to 11.5 ml corresponding to a 2.5 to 30 % increase in Vo_{2max}. This differential training response is in accordance with the results of others[50] , who during much longer training periods, even found ranges of 5 to 88 %.[50]

Possibly, the incomplete training response in some subjects prevented a significant training effect to emerge from the ANOVA. To test this assumption we computed Spearman rank correlation coefficients between the increases in Vo_{2max} of the trained subjects and the decreases in stress-reactivity from session I to session III. This yielded only two significant effects and both were related to a change in RSA activity. The more Vo_{2max} increased in the course of training, the less vagal withdrawal appeared to occur during the MS task($r = 0.56$, $p<0.05$) and the tone avoidance task ($r = 0.54$, $p=0.05$). No significant relationship between the increase in Vo_{2max} and changes in reactivity from session I to III in any of the other variables were noted, confirming the earlier conclusion from the ANOVA that training had no effect on physiological stress-reactivity. Furthermore, when the analyses were repeated using absolute levels during the tasks, no training effects emerged either.

Discussion

The aims of this study were twofold. First of all, we wanted to show that cross-sectional differences in aerobic fitness in a homogeneous sedentary population were associated with a differential physiological response to stress. Secondly, we tried to change the response to stress by having subjects actively increase their aerobic fitness through seven weeks of endurance training. We used a set of laboratory tasks that were devised to evoke substantial physiological reactivity and to show as little between and within session habituation as possible. Furthermore, we wanted these tasks to differentially influence vascular and cardiac responses since it is as yet unclear whether fitness influences these responses in a different way. The results showed that these task requirements were met. All three tasks evoked substantial cardiovascular and/or respiratory responses, which were generally as high in the second and third session as they had been in the first session. Manipulation of the cardiac/vascular balance in the blood pressure reaction was successful too. There was an increased cardiac output in response to both reaction time tasks but not to the cold pressor test. Peripheral vascular resistance was increased only during the tone avoidance task and the cold pressor test, but not during the memory search task. It is important to note that these clear differences in underlying cardiovascular dynamics could not have been detected by the measurement of mere heart

rate and blood pressure, since these increased about equally during all three tasks.

Although all our subjects reported low levels of habitual physical activity during the past year, pre-existing differences in maximal oxygen consumption values at the first session were substantial. These differences in aerobic fitness may reflect different physical activity in years further back. Furthermore, self assessment of activity over the past year may have been unreliable, resulting in a misclassification of some subjects as sedentary. However, short term recall of activity is highly correlated with true activity as assessed from diaries, and reasonably predictive of long term activity levels.[120] Habitual physical activity scores have previously been shown to be imperfectly related to aerobic fitness in much larger samples.[414, 491, 532] Alternatively therefore, the scatter in Vo_{2max} may reflect hereditary influences. Recent estimates of the genetic part in the phenotypic variance of maximal oxygen consumption have suggested that about 40 % of Vo_{2max} is genetically determined[47] , which could well account for the range found in the present study. When the pre-existing differences in aerobic fitness were brought into relationship with stress-reactivity, significant inverse relationships were found to the diastolic blood pressure response and the task-related reduction in respiratory sinus arrhythmia. There was no relationship between fitness and the inotropic β-adrenergic response to stress (PEP, SBP, CO). Recovery levels of none of the variables showed a relation with fitness, although pre-ejection period and total peripheral resistance responses suggested that hemodynamic effects of adrenaline were still present during the five minute recovery period after the reaction time tasks. Our results contrast with the lower β-adrenergic response[513, 343, 584, 129] and faster recovery found in previous studies.[94, 522, 249, 453] However, these studies compared exercisers with non-exercisers. Reactivity differences may have reflected difference in appraisal of the stressors caused by a difference in personality characteristics associated with being a sportsman, or the psychological effects of regular exercise. Since only non-exercisers were used in the present study, the effects of fitness on the blood pressure and respiratory sinus arrhythmia responses do not seem to reflect a difference in psychological make-up. More likely, the peripheral effects of psychological arousal were attenuated in the more fit subjects through differences in physiological make-up, like increased vagal tone and vascular sensitivity.

Since respiratory sinus arrhythmia is generally seen as an index of parasympathetic tone[220] , the smaller decrease in respiratory sinus arrhythmia in the more fit subjects suggests that they have superior cardiac vagal control during stress in comparison to less fit subjects. The immediate advantage of enhanced vagal tone would be a reduced heart rate response during the tasks or a faster heart rate recovery afterwards. In this study no significant effects of fitness were found on heart rate response to or recovery from any of the stressors. Nonetheless, the heart rate level during the three reaction time tasks was lower in the more fit subjects, which was largely due to their lower basal heart rate. A possible explanation for the absence of an effect on heart rate response may be that a small amount of vagal withdrawal has a strong chronotropic effect in aerobically fit subjects. In fact, stronger chronotropic effects of vagal withdrawal in subjects with low resting heart rates may be the physiological equivalent of what has been termed the Law of Initial Value.[323] Clearly, we could have tried to correct reactivity for differences in resting heart rate level. However, one may wonder why so much attention is given to

heart rate responsivity rather than the absolute heart rate levels attained during stress. In **all** studies on stress and fitness known to us, absolute heart rate level during stress has consistently been lower in the high fit subjects, although this has received much less attention than the failure to find reduced responsivity. In contrast to heart rate reactivity, absolute heart rate levels have been empirically related to the incidence of coronary heart disease in humans.[140, 293, 309, 206] and plausible mechanisms have been put forward to explain this effect.[24] Furthermore, high resting heart rates, caused partially by a low vagal tone, are also characteristic of borderline hypertensives with a hyperkinetic circulation[284, 279, 135] Therefore, low heart rate levels during daily activities, combined with a high vagal tone, may be a characteristic of fit subjects deserving more attention than task induced HR increases above the pre-task baseline.

During the stressors absolute blood pressure levels were lower in fit subjects too. In contrast to the heart rate levels however, this seemed to depend strongly on the reduced blood pressure reactivity and not on lower baseline pressures. Previously we had shown that athletes had a reduced diastolic blood pressure reactivity to stress in comparison to subjects not engaged in sports.[129] Two other studies have reported an attenuation of the blood pressure response to psychological stress in groups of fit subjects. Hull et al.[265] found endurance time on a treadmill to be negatively related with diastolic blood pressure response to a stressful task, although the diastolic blood pressure response was reduced only in the older subjects. Holmes & Cappo[254] showed a reduced diastolic blood pressure response too, using high fit subjects with a parental history of hypertension. In the present study the negative relation between aerobic fitness and diastolic blood pressure reactivity was replicated using an all sedentary group. In contrast, Light et al.[343] and Turner et al.[584] found no effect of exercise status on diastolic blood pressure reactivity. However, latter studies used short-lasting tasks in which there were non significant increases in diastolic blood pressure. The significant relation between fitness and diastolic blood pressure reactivity to our tone avoidance task suggests that the effects depend largely on the presence of an increase in the peripheral resistance. This is in agreement with the conclusion of an earlier study in more extreme fitness groups, where the lowered diastolic blood pressure responsivity could be ascribed to differences in vascular rather than cardiac reactivity.[129] Interestingly, the lowered resting mean arterial pressure that was found after fitness training could be entirely attributed to a reduction in peripheral vascular resistance.[275] Therefore, the true advantage of being fit may well reside in the response of the vessels rather than the heart.

That raises the question of what physiological mechanisms underlie a reduction of vascular reactivity in fit subjects. Aerobic fitness may influence the peripheral resistance response to stress in several ways. High and low fit subjects may differ in: 1) baroreceptor sensitivity 2) muscular tension during stress 3) structural properties of the vascular walls or the amount of capillaries 4) noradrenergic activity 5) adrenaline secretion or 6) adrenoceptor sensitivity. Since evidence for any of the other alternatives is lacking at present, we believe that the reduced blood pressure reactivity may best be explained by a difference in vascular adrenoceptor sensitivity. Although there seems to be no effect of fitness on α-adrenergic sensitivity, the vascular β-adrenergic effects are clearly potentiated in fit subjects. Infusion of physiological doses of adrenaline gives a much stronger

depressor response in fit subjects[564] , pointing to an increased sensitivity of the β-2-receptors. A clear difference in β-2-receptor density on the lymphocytes of high and low subjects have been repeatedly demonstrated[28, 335, 361] , which could well account for this phenomenon. An increased vascular β-receptor sensitivity allows diastolic blood pressure to be lower in fit subjects even when cardiac β-adrenergic activity is unchanged, which perfectly matches the data of the present study. Furthermore, it can account for the absence of fitness effects on the blood pressure response to the cold pressor test. Adrenaline is known not to change in most subjects during the cold pressor test.[417] If the differences in the blood pressure response of high and low fit subjects are related to differences in adrenaline mediated vasodilation, it is not surprising that no effects of fitness were seen during a cold pressor test. In short, enhanced vascular β-receptor-sensitivity in the more fit subjects corresponds well with the findings of the present study.

Although the relationship of fitness with vagal withdrawal and diastolic blood pressure responses during stress seem to have a plausible physiological base, it is unclear whether fitness training can be used to reduce reactivity of these parameters. Alternatively, the association is caused by concurrent effects of constitution on both aerobic fitness and stress-reactivity. To rule out such effects, subjects were submitted to a 7 weeks training program. Ideally, training might have been expected to be effective in decreasing reactivity through combined psychological (appraisal) and physiological (vagal tone, β-receptor-sensitivity) effects. Although aerobic fitness went up with a mean of 11 %, no such "ideal" effects were seen. Training did not reduce any of the physiological responses to the tasks, nor the absolute levels during the tasks. Excepting the initially low fit subjects of Holmes & McGilley[255] , who decreased their heart rate reactivity in the response to a laboratory stressors, all other longitudinal studies failed to find an effect of fitness training too.[523, 509] Speed of recovery of the heart rate after the stressor has been found to be enhanced by training in some studies[298] , but not in others.[523, 509] In the present study no effect of training was found on recovery of heart rate or any of the other variables. This study was the first to measure changes in the response of CO, TPR and RSA as a consequence of training. However, stress-reactivity/recovery of these variables was not changed by training at all.

The absence of training results clearly contrasts with the lower blood pressure reactivity seen in the cross-sectional comparison of the more and less fit subjects. The relatively low absolute increase in Vo_{2max} of 5.2 ml compared to the larger range of 30.1 ml in the correlational analysis may explain the negative findings. Training of such short duration may not have caused the required physiological adaptations. This may be complicated by the fact that there are strong individual differences in response to training. When looking at the correlations between the training-induced changes in Vo_{2max} and respiratory sinus arrhythmia, the stress-induced reduction in arrhythmia did seem to be attenuated by training in subjects with the greatest increase in fitness. A similar phenomenon was noted by Sinyor et al.[523] Once they analyzed pre-post training changes in Vo_{2max} in stead of training vs control group differences, a faster heart rate recovery was found. Changes in Vo_{2max} may also have to be high to bring about the changes in blood pressure reactivity. Although cross-sectional studies do show clear differences in β-receptor sensitivity of high and low fit subjects, two longitudinal studies

found either no change, or even a decrease in β-receptor density after two months of training.[612, 71] Vascular sensitivity to adrenaline was clearly higher in well trained men, but four months of training was not effective for changing sensitivity in a group of previously untrained men.[564] This suggests that duration of training should be long enough, and/or that absolute increases in fitness should be high enough to bring about the physiological adaptations needed to reach an effect on psychophysiological reactivity. Since training-induced changes in Vo_{2max} are larger if the initial level is lower[48] , this could mean that training will only reduce reactivity of initially low fit subjects. Alternatively, the cross-sectional studies may reflect individual differences in constitution that cannot be easily changed by fitness training programs, no matter how long the duration. These could be differences in personality, central parasympathetic/sympathetic nervous system organization, hormone receptor functioning or vascular architecture, and be located anywhere from the brain to the capillaries.

In summary, the present study found a relation between the pre-existing differences in aerobic fitness in a sedentary population and blood pressure reactivity during stress. This was not related to reduced cardiac reactivity but seemed to reflect a smaller increase in total peripheral resistance. A possible explanation for this may be a difference in adrenoceptor functioning. There was also less vagal withdrawal in the more fit subjects. This was not effective in reducing heart rate response, but absolute heart rate levels were lower during stress. Seven weeks of training did not result in a change in responsivity to the stressors, confirming other training studies done so far. A possible explanation for the discrepancy between cross-sectional and longitudinal results is that training of longer duration is needed for the physiological and psychological improvements to settle. Alternatively, it may be wrong to automatically expect an effect of training based on the cross-sectional findings. This is not a problem unique to the relation between aerobic fitness and the stress response. In spite of the cross-sectional relationship between fitness and cardiovascular risk factors, like cholesterol or blood pressure, several authors have expressed their scepticism about the possibility to induce positive changes in the risk profile by training programs.[577, 502] At the highest level - the epidemiological - it has been challenged that physical activity per se reduces the risk for cardiovascular disease. Existing cross-sectional differences in aerobic fitness predict mortality better than the current activity status.[66, 414, 531] This may suggest that aerobic fitness is the expression of an underlying healthy constitution and that only marginal health-effects will arise from short-term exercise programs. This may apply in full to the effects of fitness on the responsivity to stress. If substantial longitudinal changes in aerobic fitness do not modify psychophysiological reactivity even in low fit/high reactivity groups, then the observed cross-sectional effects may reflect a common disposition that cannot be changed by regular participation in sportive activities. We believe that more research is warranted before accepting such a harsh conclusion.

6. Regular exercise and aerobic fitness in relation to psychological make-up and physiological stress-reactivity

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Introduction

Beneficial effects of regular exercise on psychological make-up have formed a recurrent theme in psychosomatic research.[405, 179, 262, 338] Psychological characteristics often suggested to render a person "disease-prone" , like depression and anxiety[197] , have consistently been found to be lower in regular exercisers[548, 478] , and this has led to the idea that exercise could be used as a prophylaxis against stress and stress-induced disease.[253, 254, 62] However, it is unclear whether the favorable psychological profile of exercisers is due to self-selection, or whether it is caused by regular exercise. Several longitudinal studies have reported improved mood[521, 25, 98] and reductions in type-A behavior[274] , depression[388, 480, 363] , and anxiety[553, 210, 351] after a short-term program of exercise training. Unfortunately, others have failed to replicate these training effects[477, 263, 523, 302, 411, 2, 338] and even major reviews do not arrive at definite conclusions.[179, 262, 61] Present evidence suggests that beneficial effects of exercise seem to be limited to subjects who experience psychological disturbances and/or have very low fitness levels.[405, 608, 521, 480] This would question the use of exercise for stress-prevention in the population at large.

A serious problem surrounding the exercise/stress research is that dependent measures have generally been based on self-report (questionnaires), which makes the results vulnerable to subject bias. The strong societal attitudes towards the exercise as a stress-alleviator, and the fact that only volunteers can be used as subjects, may frustrate even the most rigid attempts to control for expectancy effects. A more objective index of individual susceptibility to stress may be found in the responsivity of the autonomic nervous system to a standardized psychological challenge. Activation of the autonomic nervous system and the ensuing cardiovascular responses are generally regarded as the common pathway by which stress compromises our health.[372, 385] Therefore, measuring stress-reactivity has the additional advantage of linking the possible psychological benefits of exercise more directly with its long-term health consequences.

Several studies have reported lower stress-reactivity in exercisers compared to non-exercisers[324, 255, 343, 584, 130] , and although other studies did not find any significant differences[133, 88] , only one study reported the opposite finding of high reactivity in exercisers.[324] Unfortunately, these studies were cross-sectional in nature and subjects often differed in exercise behavior as well as fitness level. Consequently, self-selection factors and differences in endowment for fitness may have caused the differences in reactivity rather than exercise behavior. Closely related to the causation issue is the question of what mechanisms mediate the hypothesized effects of exercise on psychophysiological reactivity. In particular the relative contribution of psychosocial and physiological factors is unclear. Proposed psychosocial effects of exercise include

"time-out" from daily routine, discharge of hostility, social reinforcement from training-mates, peers and family, feelings of mastery and competence, and increases in (physical) self-efficacy and global self-esteem.[179, 262, 591, 536] These psychological changes may reduce feelings of depression, hostility, and anxiety, and have a beneficial influence on the appraisal of stressful situations, such that stressors look challenging rather than threatening. As a consequence, less arousal may be experienced in a evaluative context (like mental stress testing), and psychophysiological reactivity will be found to be lower after training.

Alternatively, the beneficial effects of exercise may depend critically on training-induced changes of a physiological nature, often summarized by the increase in aerobic power. In analogy to their lower sympathetic response to physical load it has been suggested that high aerobically fit subjects may also be less responsive to emotional load.[129] More importantly, even if the autonomic nervous system responding is unaltered, the heart rate or diastolic blood pressure responses may be attenuated by the physiological characteristics of high fit subjects, e.g. a higher vagal tone and increased vasodilatory capacity (previous chapter). If these fitness-related characteristics are crucial, the high genetic contribution to fitness[47, 158] may limit the usefulness of short-term training programs in changing psychophysiological reactivity. The latter seems to be underscored by several longitudinal studies that have failed to find reduced stress-reactivity after 8 to 12 weeks of training.[523, 477, 255, 38, 511, 40, 554] On the other hand it may be argued that the previous training programs simply have been to short to induce the necessary physiological and psychological benefits. More powerful training designs may be needed to detect a reduction in reactivity. In addition, most studies have used heart rate and blood pressure as dependent variables, whereas shifts in cardiac output and vascular resistance are more likely from a physiological viewpoint.

Perhaps as a consequence of the intricate interweaving of nature-nurture and body-mind dilemmas, few studies have tested the interrelationships of fitness, stress-reactivity and psychological make-up simultaneously[324, 102, 453, 352, 260] , and even fewer have specifically looked at concomitant changes in psychological make-up and psychophysiological reactivity in the course of training.[523] The present study aims to explore these issues in more detail. First, the existence of cross-sectional relationships between aerobic fitness, psychological make-up, and stress-reactivity was assessed in an all-sedentary population. Aerobic fitness was operationalized as the maximal oxygen consumption during a maximal exercise test. In a subsequent longitudinal phase, we tested the effects of exercise training on both psychological make-up and stress-reactivity. These training effects were brought in relationship to the subjects' initial psychological make-up and fitness level. In addition, an exploration was planned of the interdependency of the training-induced changes in stress-reactivity, psychological make-up and aerobic fitness. To be able to infer robust causality of training effects, a training versus waiting-list control group comparison was extended with a training/de-training design. To lower the risk of making our training regimes too mild to detect significant effects, a long-term training group was included that trained for an 8 months period at a high intensity. It was hypothesized that:

1) High aerobic fitness will be associated with a favorable psychological profile.

2) The physiological response to a series of standardized laboratory stressors will show an inverse relation to aerobic fitness.
3) Exercise training will improve the psychological make-up and reduce physiological stress-reactivity.
4) These training effects will be stronger in subjects with the least favorable initial psychological and physiological profile.

Methods

Subjects

Subjects were recruited from the pool of male workers at the Free University of Amsterdam aged 25-40 yr. Both academic and non-academic workers were regarded eligible. 1503 persons received a recruitment letter in which they were invited to join an aerobic training program for four months. Subjects were asked to join the program only if they had been untrained during the past half year. Subjects were considered untrained when, on average, they had not been engaging in any regular exercise more than one hour per two weeks during the past six months, and preferably even longer. All subjects underwent medical examination to check their ability to join an intensive training-program, and to rule out the regular use of potentially confounding drugs (anti-hypertensives, aspirin, or lipid-lowering drugs). A total of 73 subjects applied for the experiments of which 62 met our criteria (2 subjects used β-blockers and 9 were not considered to be sedentary). Subjects were paid 125 Hfl (70$) for their participation. Informed consent with the procedures was obtained from each subject before entry into the study. The experimental protocol was approved by the Ethics Committee of the Vrije Universiteit Medical Department.

Training Groups Design

Part of the subjects were allowed to start a four months training program immediately, whereas another part of the subjects were asked to postpone training for an initial four months period, in which they functioned as a waiting-list control group. Half of the immediate starters were de-trained in the second four months period. De-training meant complete reversal to their sedentary habits within 1.5 months. The other half of the immediate starters continued their training throughout the entire eight month period (long-term training). In addition to these three training groups, there was a group of subjects who were asked to attend all three measurement sessions, although they would not partake in training. This group functioned as an overall no-training control group. To this group we added two subjects who failed to train more than twice a month on average, but were willing to complete all necessary testing. The resulting design is shown in figure 3. The four-months trainers were randomly assigned to the de-training or postponed training groups. Participation in the long-term training and the no-training control groups was based on self-selection.

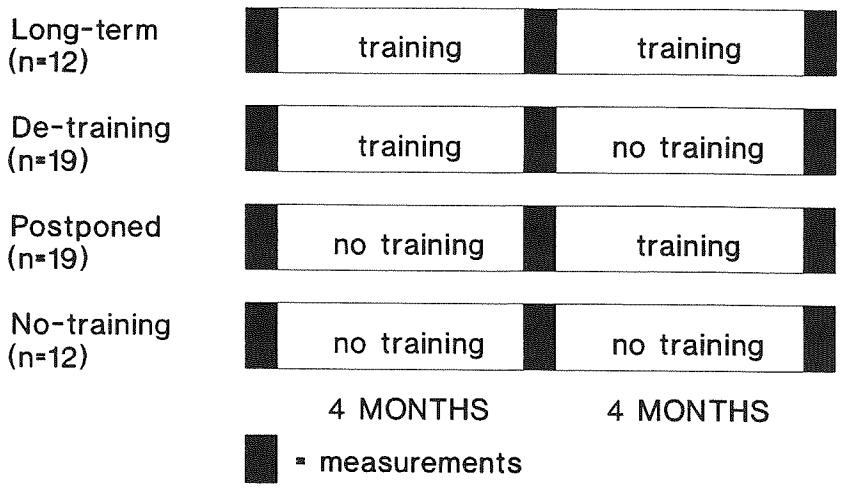

Figure 3: The training group design. The long-term training group trained throughout the 8 months period. The de-training group trained for 4 months and then de-trained. The postponed group remained untrained during the first 4 months and trained during the second four months. The no-training group remained untrained throughout the whole 8 months period. Measurements on all relevant variables were taken when subjects were 0, 4 or 8 months into their respective treatments.

Procedure

Psychological and physiological laboratory testing was performed at the start of the study (0 months), after the completion of the first training period (4 months), and after the completion of the second training period (8 months). To control for diurnal variations in the physiological variables, all laboratory testing took place between nine and twelve o'clock in the morning. Subjects were asked not to smoke or drink coffee/tea on the morning of the experiment. At the start of the laboratory session subjects voided and filled out the first half of the set of psychological questionnaires (detailed below), followed by a short interview on their physical activity habits. After 45 minutes subjects voided again and were hooked up for psychophysiological testing. Pre-stress resting values of the cardiovascular variables were assessed during the last 5 minutes of a 15-minute period of sitting quietly in a dimly-lit sound-shielded room. Next, the subjects performed two 10-minute reaction time tasks, identical to those used in the previous chapter. Both reaction time tasks were extensively explained to the subjects and they were given two 1-minute practice trials. Task engagement made high by competition for a substantial financial bonus. Subjects were member of a team of five subjects that could earn Dfl 500,- (270$) or nothing at all, depending on their joint performance. Points gained on both active coping tasks were written down on a clearly visible blackboard in the experimental room. Subjects were explicitly reminded of the fact that, if they were to

fail, the other four members would loose money too. Task difficulty (criterion reaction time) was silently adjusted during the tasks, and sustained effort was needed to maintain performance. Furthermore, the criterion was made more stringent at retesting after 4 and 8 months to reduce habituation to the tasks.

In a two minute anticipatory period before the start of the stressors, subjects watched a clock counting down the remaining seconds. At the end of each task subjects were allowed three minutes of recovery. Physiological recording was continued throughout these anticipatory and recovery phases. The reaction time tasks were followed by a cold pressor test, where subjects were required to keep their hand immersed in cold water (4^{o}) for 2 minutes. Fifteen minutes after this last stressor, an additional 8-minute resting period was recorded (post-stress rest). Following the post-stress rest subjects voided again and filled out the second set of questionnaires. After a short break, the laboratory session was concluded with a maximal exercise test on a bicycle ergometer. Post-training measurement of psychological and physiological variables was scheduled to fall between 2 and 8 days after the last exercise session.

Physiological variables

An electrocardiogram (ECG) was obtained from disposable pregelled Ag-AgCl electrodes (AMI type 1650-005 Medtronic) that were placed on the sternum and the lateral margin of the chest, according to the standard lead II configuration. The ECG was recorded using the Nihon Kohden bioelectric amplifier (AB 601G) with a time constant of 0.1 sec and a 30 Hz high cut-off filter. The thorax impedance (Z) was recorded with the Nihon Kohden Impedance Plethysmograph (AI-601G) with a tetrapolar spot electrode system.[43] Current electrodes were placed on the back of the subject at the height of the cervical vertebra C4 and thoracical vertebra T9 respectively, imposing a current of 350 μA, with a frequency of 50 KHz and an output impedance > 40 Ohm). Measuring electrodes were placed directly below the laryngeal cartilage projection (Adam's apple) and over the tip of sternum. The base thorax impedance (Z_0) was continuously displayed and recorded by the experimenter every minute. Thorax impedance change (ΔZ) was recorded with the Nihon Kohden Differentiator (ED-601G), using a time constant of 5 ms and a high frequency cut-off of 75 Hz. This yielded the first derivative of the thorax impedance, $\delta Z/\delta t$. The phonocardiogram (PCG) was recorded using a Siemens-Elema AB microphone placed over the heart between the third and fourth ribs. PCG was amplified by the Nihon-Kohden PCG amplifier (AS 601H). The respiration signal was recorded with a mercury strain-gauge strapped around the waist at a level 7 cm above the umbilicus. Frequencies above 30 Hz in this signal were removed by a hardware filter.

From the ECG, ICG, PCG and respiration tracings we computed minute-mean values for heart rate (HR), respiratory sinus arrhythmia (RSA), pre-ejection period (PEP) and cardiac output (CO) according to the methods that were described in detail in the previous chapter. Blood pressure was measured every two minutes, and at least once during each separate condition, with a Dinamap Vital Signs Monitor (Critikon model 845 XT). Combining the blood pressure measurements with the cardiac output value of the corresponding minute, total peripheral resistance (TPR) could be estimated by the

formula:

$$TPR = (MAP/CO) * 80 \text{ (in dyne-seconds/cm}^5\text{)}$$

Although the evidence for the interindividual validity of impedance derived stroke volume is increasing, the intra-individual approach was still favored in a recent committee report[512] , and little data is available on reliability of impedance derived stroke volume over repeated measurements. Since we were mainly interested in reactivity, percentual changes from the post-stress resting level were used for cardiac output and total peripheral resistance rather than absolute values.

Three ml of the urine was taken from each sample, adjusted to a pH of 3.0 and stored at -18^{o}C until analyzed by high-performance liquid chromatography according to the method described by Westerink & Koolstra.[606] A small amount of water or orange juice was sometimes provided to ascertain adequate urine production. Urinary excretion of noradrenaline, adrenaline and dopamine was expressed in pmol.min^{-1} per kg body weight. Catecholamine reactivity was measured by comparing the pre-stress with the post-stress excretion rates. Since noradrenaline and adrenaline secretion are subject to circadian effects, we also computed the ratio of (nor)adrenaline with dopamine that was recently suggested as an alternative to creatinine.[606]

Psychological variables

Assessment of psychological make-up included questionnaires on personality, negative affect, behavioral style, self perception, and short-lasting mood states. All questionnaires had been translated and validated for use on a Dutch population. The choice of psychological variables was based on previous demonstration of a relationship between the variable and 1) susceptibility to disease, 2) psychophysiological reactivity 3) fitness level or exercise behavior.

Personality was assessed with the Dutch Personality Questionnaire (DPQ).[360] This questionnaire measures Inadequacy (neuroticism), Social Inadequacy (introversion), Rigidity, Hostility, Selfsufficiency, Dominance and Self Esteem in the normal population. Since hostility is repeatedly mentioned as the crucial trait associated with high reactivity and cardiovascular disease, additional assessment of hostility was performed using the 66-items proposed by Buss & Durkee.[70] Scores on subscales assault, indirect hostility, irritability, negativism, resentment, suspicion, verbal hostility and guilt were summed to yield a total hostility score. In addition, the subjects filled out the Jenkins Activity Survey for Type A behavior (JAS)[13] and the Maastricht Questionnaire for Vital Exhaustion[14] both of which have been shown to predict cardiovascular pathology.

Individual differences in coping style were assessed with the Utrecht Coping List (UCL).[500] This list is based on the work of Westbrook[605] and has subscales for seven styles of habitual coping with stressful situations: Active Problem Solving, Palliative Coping, Problem Avoidance, Depressive Responding, Comforting Cognitions, Social Support Seeking, and Expressing Emotions. Since cardiovascular reactivity is particularly prominent in anger provoking situations, coping with such situations was

measured specifically with a scale based on the Spielberger Anger Expression Scale.[542] Subjects are asked how they generally respond when angered. They indicate whether they control their anger inwards (e.g. "I try to calm myself") and outwards ("I try to control my voice") or express their anger inwards ("I'm boiling inside, but don't let it get noticed") or outwards ("I start shouting at people"). The questionnaire yields scores for Controlled Anger In, Controlled Anger Out, Anger-In, and Anger-Out.[366]

Negative affect was measured with Zung's Self Rating Depression Scale[620, 116] and the Spielberger inventories for Trait Anxiety and Trait Anger.[455, 454] Current psychosomatic complaints were registered with the Hopkins Symptoms Checklist.[109, 359] The items from the Physical Self Efficacy[487] and Rosenberg Self Esteem[474] scales items were merged into one questionnaire, and interspersed with several filler items to remove some of the obvious emphasis on personal worth in both questionnaires.[236] The extent to which the subjects consider life events to be under internal rather than external control was measured with a short version of Rotter's scale for Internal Locus of Control.[12] Expectations on the benefits of the training program, and beliefs about the importance of exercise in general, were assessed with a Likert type 7-point rating scale, on which participants indicated: 1) Their present physical fitness compared to that of a) friends, b) family, c) colleagues d) other men in general 2) How much they expected their fitness to change (before training) 3) How much they felt their fitness had changed (after training) and 4) How important they felt it was for people to exercise regularly.

Mood was assessed with a shortened version of the Profile Of Mood States.[599] POMS subscale scores on the Depression-Dejection, Fatigue, Anger-Hostility, and Tension-Anxiety items were summed to yield a negative mood index. The sum of Vigor-Activity and Friendliness was used to index positive mood. The POMS was filled out at home at the end of a weekend day and two representative work days. Subjects were asked to rate their mood over the past day.

Shortly before the start of the laboratory session, subjects filled out the state versions of the Spielberger inventories for anxiety and anger.[455, 454] Directly after the reaction time tasks, the subjects were asked to indicate the amount of effort they had spent on the tasks and how distressed they had felt. The visual analog scale used by Meijman et al.[395] was used for this purpose.

Physical activity status

Only subjects who were untrained were asked to join the program. However, even in a population of non-sportsmen, large individual differences in habitual activity may occur, for instance because of work-related activities, the use of a bicycle for transport, or gardening. Classification of individual differences in average energy expenditure were measured with the 7-day recall interview according to Blair et al.[34] To increase reliability of recall, subjects were encouraged to use their agendas to re-trace last weeks moderate (bicycling, walking) and heavy (running, mowing the lawn) physical activities. Total energy expenditure was expressed in $kcal.kg^{-1}day^{-1}$. Additional assessment of their recent habitual activity status was done with a six-months version of the Minnesota

leisure time activity questionnaire (LTPA).[568] The questionnaire was slightly adapted to reflect activity patterns in the Netherlands (e.g. more elaborate information on bicycling as a means to get to work, school, friends etc). Subjects received the activity questionnaire by mail a week prior to the laboratory session. During a 15 minute interview at the start of the laboratory session a detailed check-up of the reported intensity and duration was performed for each activity checked. Finally, long term history of sports participation was measured by having the subjects recall the number of hours weekly spent on competitive or recreational sports (including solitary running) since high school.

Maximal exercise testing

To determine aerobic fitness, all subjects performed a supramaximal exercise test on a bicycle ergometer, according the nine minute protocol described in the previous chapter. Briefly, maximal oxygen consumption was estimated from the heart rate response to submaximal exercise. During the final minutes of the test a load was imposed that required 20 % more oxygen consumption than the estimated maximum of the subject. Peak oxygen consumption measured during this supramaximal step was the subjects true maximal oxygen consumption. The test was stopped once oxygen consumption did not rise any further, or if the subject gave up. During the test, the subject breathed through a high velocity, low resistance mouthpiece with minimal dead space that shunted all the expired air into a flow meter (Jaeger Screenmate). Exhaled air was collected in a homogenization bag and samples of homogenized air were fed into oxygen and carbondioxide sensors (Jaeger). This procedure yielded minute volumes of carbon dioxide production and oxygen consumption. These volumes were converted to volumes in standardized conditions (0^{o}C; 760 mmHg; dry).

Height and body weight were determined before the exercise test with subjects wearing only shorts. Absolute maximal oxygen consumption expressed in liters per minute was divided by body weight, yielding a weight corrected maximal oxygen consumption in milliliters per kg body weight, that will be used as the main index of aerobic fitness (Vo_{2max}).

Training

The training program consisted of outdoor running and indoor fitness training, depending on weather conditions. All training sessions started with some warming up exercises for ten minutes. Subjects then either ran a distance of 3 to 10 km (progressively longer distances in the course of training), or spent their time indoor on a combination of conditioning exercises (three minute bouts of running, jumping in place, climbing up and down racks, ropes, etc.), aerobics and soccer/basketball games. All training was at a self-chosen frequency of 1.5 to 2.5 hours a week, except for the long-term trainers who trained at a minimal frequency of 2.5 hours a week. Training frequency was deliberately allowed to vary to enhance the power of training-dose to training-effect analyses. Group training sessions were supervised by a trainer who also kept record of attendance. During the last months of their training, subjects in the long-term training group trained individually. Intensity of training (running speed, number of repetitions) was kept at about 70%

of the subjects maximal capacity, by regularly checking the subjects pulse rates against their maximal heart rate.

Data analysis

Per variable, all available samples were averaged to yield 11 condition means reflecting the pre-stress rest (PRE), Tone Avoidance task (TA), Memory Search task (MS), Cold Pressor test (CP), anticipation to (3x) and recovery from (3x) these tasks and the post-stress rest (POST) condition. Reactivity to the tasks was expressed in simple change scores by subtracting the post-stress resting level from the levels attained during these conditions. A similar procedure was used for the anticipatory reactivity scores. A priori we decided to use the post-stress resting value as a baseline rather than the pre-stress value, because some anticipatory physiological responding to the task session could be expected. Recovery was defined as the decrease from task level to the level attained during the last minute of recovery.
Several questionnaire scales were negative skewed due to a predominance of low scores. These scales were log-transformed before statistical analysis. A similar transformation was necessary for the catecholamines and respiratory sinus arrhythmia. For readability, the original (untransformed) values will be used in the tables and figures.

The effects of the laboratory stressors on the physiological variables at the start of the study were tested with repeated measurements MANOVA, using the multivariate approach to avoid the problem of false positives.[590] Cross-sectional associations between fitness, psychological make-up and reactivity scores were tested with simple Pearson correlation. All correlations were tested against a two-tailed significance level of 0.01, unless stated otherwise. To outline training effects on the physiological response to the laboratory manipulations at 0, 4 and 8 months, all variables were separately submitted to multivariate analyses of variance with group (4) as a between subjects factor, months (3) as the repeated measurement factor and, where appropriate, conditions (11) as a second repeated measurement factor. If initial group differences were found, the level of the variable at the first measurement was used as a covariate. Before all testing, homogeneity of all variates was ascertained by inspection of the Boxplots and the Cochrans statistic. Tukey HSD was used to follow up on significant main and interaction effects (p's <0.05).

Results

Cross-sectional analyses

Initial assessment of Vo_{2max} showed that that subjects were moderately fit on average, although large individual differences in fitness were seen (see table 5). Weekly energy expenditure estimated from the 7-day recall remained well below that of regular exercising subjects[34] and inspection of the habitual activities over the past year showed no systematic training activities. Some recreative sports were practiced by some subjects, and even some running, but the frequency of these activities was low or entirely limited

Table 5: Mean, standard deviation and range of fitness and physical activity variables in the complete sample (N=62), at the start of the study (0 months).

	Mean	SD	Range
Age (yr)	32.8	4.1	24 - 40
Length (cm)	183.4	5.0	173 - 194
Weight (kg)	76.6	7.3	61.4 - 95.3
VO_2max (l)	3.50	0.50	2.51 - 5.05
VO_2max ($ml.kg^{-1}$)	45.9	6.5	29.7 - 63.3
Habitual activity			
7-day recall ($kcal.kg^{-1}.day^{-1}$)	38.5	2.1	36.1 - 45.3
Leisure time activity ($kcal.day^{-1}$)	257.8	140.0	49.2 - 521.7
Bicycling (minutes/day)	19.8	20.1	0 - 90
Past sports participation (hours/year)	33.6	34.8	0 - 122

to outbursts during holidays (e.g. skiing, swimming). Individual variation in energy expenditure, both in the 7-day recall and the LTPA, was mainly due to differences in the daily amount of bicycling. The average minutes spent on bicycling per day reported during the 7-day recall was introduced as an additional variable. Energy expenditure computed from either 7-day recall or LTPA was not related to aerobic fitness. Only bicycling ($r = +0.44$) and the minutes spent on sports or other vigorous activities during the past half year showed significant correlation with Vo_{2max} ($r = +0.37$). Although spontaneous recall of sports behavior over 10 to 15 years can at best be considered a crude index of past sports behavior, a remarkable pattern was found. Forty-eight percent of our subjects reported (vigorous) sports behavior up till a few years ago, and only 16 % reported to have been completely sedentary since high school or their obligatory term in the army. This suggests that, although subjects could be considered untrained at entry to the study, many of them had a history of exercise participation. comparable to that of the general population.

Psychophysiological reactivity

Figure 4 displays the average heart rate and blood pressure response of all subjects to the first laboratory session. Exposure to the three stressors yielded significant changes in HR ($F(10,52)=31.20$, $p<0.0001$), SBP ($F(10,52)=33.69$, $p<0.0001$), and DBP ($F(10,52)=32.82$, $p<0.0001$). Post-hoc comparison of the condition means showed that HR, DBP, and SBP were significantly elevated above the post-stress resting value during all three stressors. A significant elevation in HR, DBP, and SBP was already seen before the start of the tone avoidance and memory search tasks, when a clock counted down the remaining time. Only blood pressure showed a significant effect of anticipation during the cold pressor test. After each task HR fully recovered to its resting level, but SBP and DBP recovery was incomplete. Anticipatory levels during the memory search and cold pressor conditions may have partly reflected this incomplete recovery. In contrast to what was seen for HR and SBP, the pre-stress resting value of the DBP was significantly

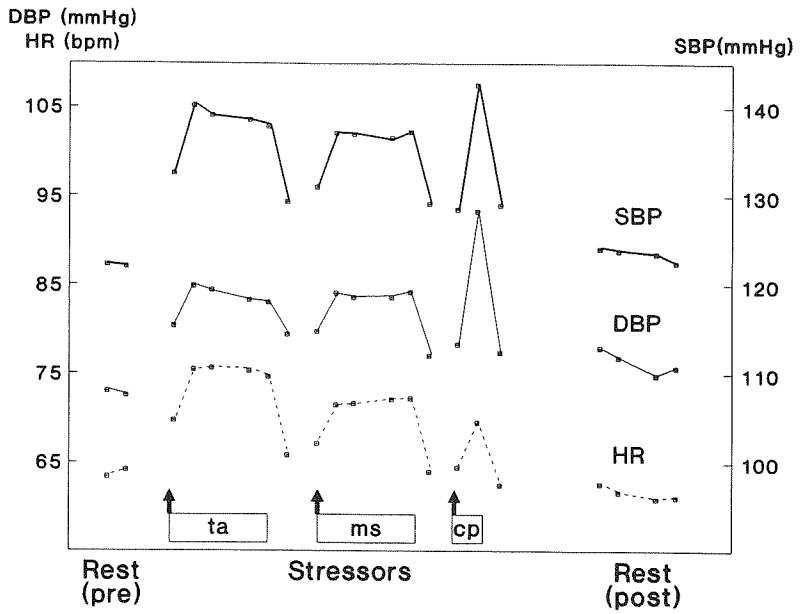

Figure 4: Heart Rate and Blood Pressure levels during the Tone Avoidance task (TA), the Memory Search task (MS) and the Cold Pressor test (CP). Before the actual start of the tasks, a clock counted down the remaining 120 seconds. This anticipation period is indicated by the up arrows. Each task was followed by a three minute recovery period. Resting levels were measured both 5 minutes before (pre) and 15 minutes after the stressors (post).

lower than the average post-stress resting value. Since separate examination revealed a decreasing trend for DBP even within the post-stress condition, only the last four minutes were used to compute reactivity.

Figure 5 displays the main variables derived from impedance cardiography. The PEP showed a clear conditions effects ($F(10,52)= 5.81$, $p<0.001$). Post-hoc comparison of the condition means showed that PEP shortened significantly in response to the two reaction time tasks, but not during the cold pressor. A significant shortening of PEP, signaling increased β-adrenergic drive, was also seen during anticipation to the two reaction time tasks, but the effect was not as strong as during actual task performance. Some recovery took place after the tasks, but the PEP remained well below resting values. The long PEP during the cold pressor test, as well as during its anticipation and recovery phase does not necessarily suggest that no β-adrenergic drive was present. Instead it may reflect the increased afterload on the heart, caused by the strong increase in arterial blood pressure.

There was a significant effect of conditions on the percentual change scores for the CO ($F(9,46)=8.03$, $p<0.001$) and the TPR ($F(9,46)=18.41$, $p<0.001$), that mainly reflected a different response to the reaction time tasks on the one hand, and the cold pressor test on the other. During the cold pressor test TPR was much higher than during any of the other conditions, whereas exactly the opposite effect was seen for the CO. The decrease

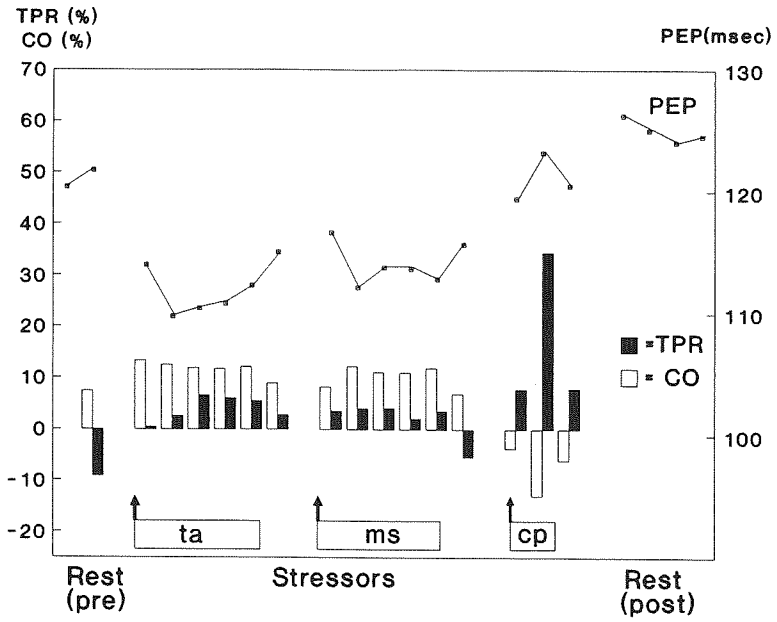

Figure 5: Pre-Ejection Period, Cardiac Output and Total Peripheral Resistance in response to the Tone Avoidance task (TA), the Memory Search task (MS) and the Cold Pressor test (CP). During a two minute anticipatory phase before the actual start of the task (indicated by the up arrows), a clock counted down the remaining seconds. Each task was followed by a three minute recovery period. Absolute Pre-Ejection Period values are given for all conditions, but Cardiac Output and Total Peripheral Resistance were expressed as a percentual change from the post-stress resting level.

in CO during the cold pressor test was a consequence of the strong increase in peripheral vascular resistance, which reduced stroke volume. Interestingly, the rise in vascular resistance was already present before the actual start of the cold pressor. Apparently, anticipatory responding depends on the type of the imminent stressor, and is not limited to cardiac β-adrenergic activity. Neither TPR nor CO showed a differential response to the two reaction time tasks, or their anticipation and recovery phases. separate testing of the change scores against zero ("no effect hypothesis") showed that the CO was significantly increased above the post-stress level at pre-stress and throughout the two reaction time tasks, whereas it was decreased during the cold pressor test ($p's < 0.004$). The change in TPR was significant only at pre-stress rest and during the cold pressor test. The higher post-stress TPR, in comparison to the pre-stress resting level, corresponds to the higher post-stress DBP seen previously. This phenomenon may represent a gradual increase in vasoconstriction over the task session due to prolonged stress, as has been reported before,[401] or it may be an after effect of the cold pressor.

Figure 6 displays the changes in respiration rate and respiratory sinus arrhythmia. Both RR ($F(10,52)= 7.21$, $p<0.000$) and RSA ($F(10,52)= 6.00$, $p<0.001$) showed a clear conditions effect. Post-hoc comparison of the condition means showed that RR increased significantly in response to the two reaction time tasks, but not during the cold pressor. Some increase in RR was already seen during the anticipatory phases, but only

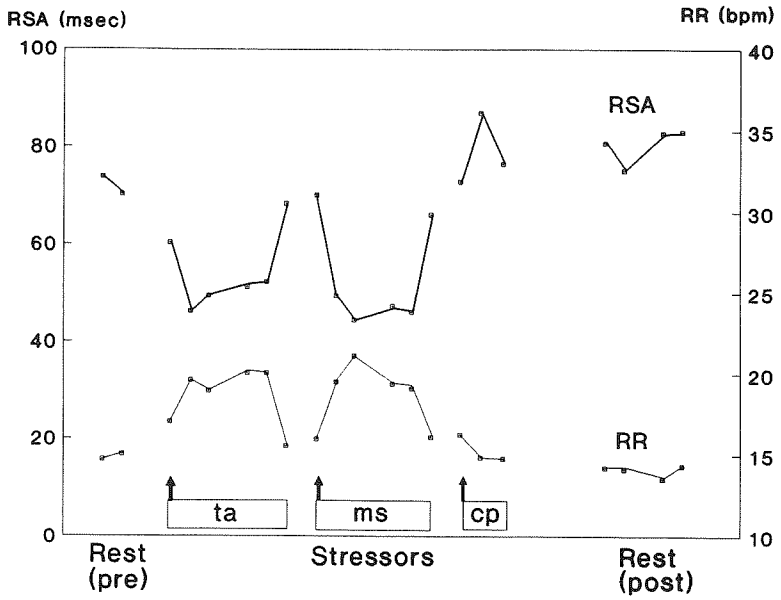

Figure 6: Respiration Rate and Respiratory Sinus Arrhythmia during the Tone Avoidance task (TA), the Memory Search task (MS) and the Cold Pressor test (CP). Each task was preceded by a two minute anticipatory phase (indicated by the up arrows) and followed by a three minute recovery period. Resting levels were measured both 5 minutes before (pre) and 15 minutes after the stressors (post).

anticipation to the tone avoidance task raised the RR significantly. Respiration rate rapidly recovered to the resting level after the reaction time tasks. A virtual identical response pattern was seen for the RSA, although the direction of the response was reversed. The decrease in RSA suggests a decrease in vagal control over the heart during the reaction time tasks. The increased RR was partly responsible for this. In all conditions, RR and RSA showed a significant inverse relation (r's between -0.47 and -0.67). In addition, changes in RSA and RR were significantly related during both tone avoidance ($r = -0.52$) and memory search task ($r = -0.38$). To remove the influence of RR, residual reactivity in RSA was computed by partialling out concurrent changes in RR. The residual RSA reactivity scores (RSA-red) will be used as extra variables in further analyses.

Comparison of pre- to post session urinary catecholamine excretion yielded a significant effect for adrenaline only ($F(1,61)=12.75$, $p<0.005$). At the end of the session adrenaline excretion was almost twice as high (1.03 $pmol.kg^{-1}.min^{-1}$) as before the start of the session (0.56 $pmol.kg^{-1}.min^{-1}$) This increase in adrenaline excretion reflects the cumulative effects of all conditions. In combination with the cardiovascular responses detailed previously, it can be concluded that the three tasks had triggered substantial physiological reactivity.

Table 6: Mean, standard deviation and range of scores on the psychological questionnaires and their correlation to several fitness indices. The descriptives and correlations were computed using data from the complete sample (N=62) at the start of the study (0 months).

Variable	Mean	SD	Range	VO_{2max}	Body Fat	SBD	DBD	HR
Dutch Personality Questionnaire								
-Neuroticism	9.0	6.7	0 - 33	.06	-.17	-.27	-.10	-.04
-Social Inadequacy	9.9	6.5	0 -27	.03	.08	.07	.12	-.04
-Self Esteem	27.3	5.3	12 - 37	-.04	.21	.13	.14	-.02
-Rigidity	19.5	6.6	5 - 36	-.00	.08	-.06	-.01	-.02
-Hostility	15.5	6.6	3 - 34	-.00	.13	-.13	-.20	-.09
-Selfsufficency	9.4	3.9	2 - 18	-.13	.38*	.16	.19	.05
-Dominance	16.4	5.4	4 - 30	-.27	.23	.04	.08	.12
JAS	12.8	4.4	4 - 22	-.01	-.00	-.08	.05	.10
Buss-Durkee Hostility	28.9	7.7	3 - 62	-.12	.07	-.26	-.24	-.07
Anger Expression								
-Express Anger In	33.6	6.6	19 - 48	.07	-.23	-.15	.01	.07
-Express Anger Out	29.6	5.7	21 - 50	-.04	-.06	-.09	-.10	-.21
-Control Anger In	31.6	6.9	13 - 44	-.07	-.08	-.03	-.07	-.05
-Control Anger Out	43.5	6.8	26 - 57	-.01	.22	.06	.10	-0.12
Trait Anger	15.6	3.4	10 - 26	-.17	.08	-.09	-.04	-.01
Trait Anxiety	36.9	8.0	24 - 56	.09	-.07	-.21	.09	.14
Vital Exhaustion	8.4	7.4	0 - 33	.09	-.25	-.36*	-.04	.03
Zung Depression	42.8	6.2	31 - 61	.00	-.01	-.09	.15	-.08
Internal Locus of Control	7.2	3.2	0 - 16	.09	-.05	-.20	-.04	.05
Self Esteem Scale	80.2	9.8	40 - 98	-.17	.23	.13	.06	.02
Physical Self Efficacy	49.4	5.2	32 - 65	-.10	.18	.34*	.14	.05
Utrecht Coping List								
-Active problem solving	18.8	3.1	12 - 26	-.03	-.04	-.13	-.17	-.12
-Problem Avoidance	16.6	2.9	8 - 24	-.01	-.22	-.14	-.00	.15
-Depressive Responding	11.7	2.9	7 - 23	.06	-.03	-.16	.00	.00
-Palliative Coping	17.3	2.9	11 - 26	-.19	.00	.02	-.07	.14
-Comforting Cognitions	11.6	2.6	6 - 17	.11	-.15	.08	-.00	-.01
-Social Support Seeking	13.6	3.0	6 - 22	.08	-.18	-.04	-.24	-.14
-Expressing Emotions	6.3	1.3	3 - 11	-.17	.04	.06	-.11	.02
Psychosomatic Complaints	19.4	11.8	0 - 74	-.03	-.06	-.23	-.03	.22
State Anxiety	36.2	6.0	26 - 50	.08	.02	-.02	.25	.35*
State Anger	11.7	2.9	6 - 16	.09	.22	-.03	.29	.00
Negative Mood (work)	11.2	10.8	0 - 54	.18	-.18	-.21	-.16	.01
Negative Mood (wknd)	12.5	10.8	0 - 66	.05	-.01	-.23	-.19	-.18
Positive Mood (work)	15.2	4.7	4 - 27	-.26	.33*	.21	.10	.11
Positive Mood (wknd)	14.4	4.2	2 - 24	-.26	.26	.14	-.00	.12

*) $p < 0.01$

Psychological make-up in relation to aerobic fitness

Comparison of the scores on the Dutch Personality Questionnaire (DPQ) to published norm scales for Dutch males[360] , suggested that our subjects had a "normal" personality profile (see table 6). Furthermore, as a group, subjects did not report more negative mood than was found in comparable samples of adult males.[599] Contrary to our

hypothesis, Vo_{2max} was not related to any of the psychological variables measured. Furthermore, correlation of the questionnaire scores with body mass index, resting HR or BP also failed to yield evidence for a systematic link between psychological make-up and these alternative indices of aerobic fitness. The failure to find an association between fitness and psychological make-up was not likely due to a lack of between-subjects variance in the psychological variables. As with fitness, there was a large interindividual scatter in questionnaire scores, with standard deviations as large as 34 % of the mean on average. The standard deviations were well in accordance with those found in much larger samples of the Dutch population[455, 454, 500, 360] suggesting that the variance in our questionnaire scores was comparable to that of the general population. Furthermore, many significant correlations were found between the psychological questionnaire measures themselves. For example, neuroticism (DPQ) was associated with most other indices of negative affectivity, e.g. Zung depression (r = +0.38), psychosomatic complaints (r = +0.44), trait anger (r = +0.49), trait anxiety (r = +0.50) negative mood at work (r = +0.37) and with low self esteem on either DPQ (r = -0.44) or SES scales (r = -0.52). These correlations are again in accordance with those found in much larger samples.[500, 360, 602]

Psychophysiological reactivity in relation to aerobic fitness

There was no significant relationship between Vo_{2max} and HR reactivity to any of the tasks, or to any of the anticipatory periods. In addition, Vo_{2max} was unrelated to the task-induced shortening of the PEP, RSA or RSA-red. If anything, HR reactivity tended to be higher in the more fit subjects, particularly during the memory search task (r = +0.31). However, resting levels of HR were lower in the more fit subjects at pre- (r = -0.36) and post-stress rest (r = -0.33) and after recovery from tone avoidance (r = -0.33). In accordance with the law of initial values, the higher reactivity of more fit subjects may have been due to their lower resting levels. This was not true. When adjusted for their lower baseline value, more fit subjects appeared to have significantly higher HR reactivity during both memory search (r = +0.41) and tone avoidance (r = +0.36) tasks. After baseline adjustment, reactivity scores for PEP, RSA, or RSA-red still showed no relation to fitness.

The more fit subjects did show a larger decrease in the HR during recovery from both tone avoidance (r = +0.40) and memory search tasks (r = +0.34). However, HR reactivity to a task strongly determined the subsequent fall in HR, and correcting recovery scores for task levels removed the effect of fitness on recovery. Therefore, it is unclear whether rapid HR recovery in the more fit was a consequence of being fit, or simply followed from the slightly higher HR reactivity. Overall, HR, PEP and RSA results did not give support to the idea that either cardiac β-adrenergic responsiveness or vagal withdrawal during stress was lower in the more fit subjects.

Even more surprising were the findings on systolic and diastolic blood pressure reactivity, that were both **higher** in the more fit subjects. These associations are graphically depicted in figure 7. Significant positive correlation coefficients were found between the Vo_{2max} and the SBP reaction to the tone avoidance (r = +0.38) and memory

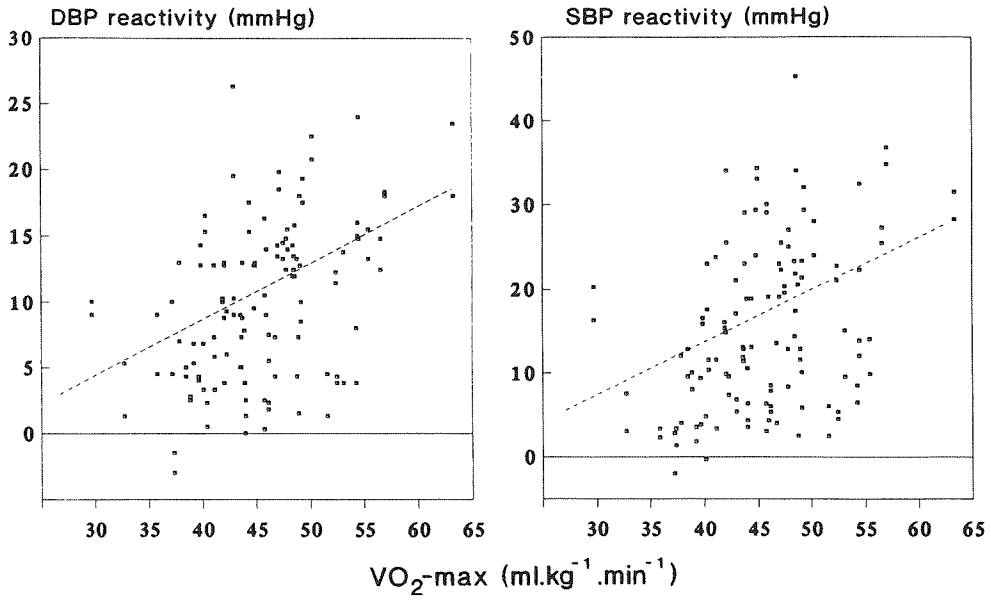

Figure 7: Systolic and Diastolic blood pressure reactivity in relationship to maximal oxygen consumption per kg body weight (Vo_{2max}). Reactivity to both tone avoidance and memory search task is plotted in one frame.

search (r = +0.42) tasks. SBP responses during anticipation to the memory search task also tended to be higher in the more fit subjects (r = +0.32). Adjusting SBP reactivity for the resting level did not influence these results, which is not surprising, since fitness and SBP level were unrelated. The fall in SBP during the recovery from the memory search task was larger in the more fit subjects (r = +0.36), but again this recovery effect was due to the higher reactivity, as had been the case with the HR. Diastolic reactivity to the tone avoidance (r = +0.43) and memory search (r = +0.46) tasks were also higher in the more fit. Although pre- (r = -0.25, p=0.05) and post-stress (r = -0.24, p=0.05) resting levels of DBP tended to be lower in the more fit, adjusting for baseline values had negligible influence on the correlation with fitness. In spite of the positive association between blood pressure reactivity and Vo_{2max}, neither CO nor TPR response was significantly related to Vo_{2max}. In addition, there was no evidence of a relationship between Vo_{2max} and the pre- to post session changes in urinary adrenaline or noradrenaline excretion. Therefore, the higher blood pressure reaction in the more fit could not be coupled to a distinct difference in vascular versus cardiac, or in adrenergic versus noradrenergic reactivity.

The association of fitness with blood pressure reactivity was limited to the two tasks evoking psychological stress. No relation was found between fitness and the response to the cold pressor test, that predominantly reflects a physical reflex. This suggests that the relationship between fitness and reactivity may have been confounded with differences in the psychological make-up of our subjects. When we examined the relationship between psychological variables and the blood pressure responses to stress, surprisingly low

correlations were found. In fact, none of the cardiovascular variables were related to any of the psychological parameters that might have been expected to relate to reactivity, e.g. neuroticism, type-A behavior, anger-out and hostility. Only the stress-induced increase in urinary catecholamine excretion during the stressors was associated with the psychological make-up in a strikingly systematic way. Reactivity of both catecholamines were significantly related to Buss Durkee hostility (r_{NA}=-0.37; r_{A}=-0.34), UCL depressive responding (r_{NA}=-0.41; r_{A}=-0.34), and negative mood at work (r_{NA}=-0.35; r_{A}=-0.43), and at home (r_{NA}=-0.41; r_{A}=-0.38), such that increased catecholamine excretion was associated with a favorable psychological profile. In addition, high noradrenaline excretion was associated with high dominance (r= 0.34), and little psychosomatic complaining (r= -0.35), and high adrenaline excretion was paired to a positive image of self (r= 0.34) and low scores for trait anger (r= -0.34), trait anxiety (r= -0.36), vital exhaustion (r=a -0.35) and UCL problem avoidance (r= -0.40). Correcting for dopamine excretion rendered the correlation between psychological variables and noradrenaline reactivity insignificant, but the correlations with the adrenaline response remained intact. In general, the pattern of correlations suggest that high catecholamine excretion during stress was associated with a favorable personality profile. However, this phenomenon was unrelated to the higher blood pressure response in the more fit subjects, since fitness was not associated with either psychological make-up or catecholamine excretion.

Directly after the tasks, subjects were asked to point out on a visual analog scale how much effort they had spent on the task, and how distressed they had felt. During the cold pressor test, self-reported distress was associated with high DBP (r = +0.53) and HR reactivity (r = +0.42). During the reaction time tasks however, distress was associated with significantly lower systolic blood pressure responses (r_{TA} = -0.35 ; r_{MS} = -0.41). The negative relation between distress and SBP responsiveness was already seen during the anticipatory periods (r_{TA} = -0.44 ; r_{MS} = -0.37). Heart rate reactivity to the tone avoidance task was also lower if distress was high (r = -0.50). In contrast to distress, self-reported effort was associated with high heart rate reactivity to the tone avoidance (r = +0.36) and memory search (r = +0.53) tasks. Since self-reported effort was related to reactivity, the reactive subjects might have been the most involved in the tasks. On the other hand, those who felt distressed, or even annoyed, were low reactors, perhaps because they had given up trying to get a high score. The lack of task involvement may have been less prominent in the younger subjects, since age was associated with lower DBP reactivity to the tone avoidance task (r = -0.42). In addition, various near significant relations were found between performance and reactivity, suggesting that differences in performance also contributed to differences in reactivity. To control for these various effects, multiple regression analysis was undertaken, in which we predicted reactivity from Vo_{2max} after forcing age, reaction time, percentage correct, total points scored, self-reported effort and distress into the equation. There was no noticeable effect of removing these confounders on the fitness to DBP reactivity or fitness to SBP reactivity relationships. Therefore, the association between fitness and blood pressure reactivity was not due to differences in age, self-perceived effort/distress or performance. In fact, when stepwise regression was performed only the amount of self-reported distress contributed to the prediction of reactivity over and above the effect of VO2max alone. Together,

VO2max and self-reported distress explained 24% of the variance in DBP reactivity and 30% of the variance in SBP reactivity.

Longitudinal analyses

During the longitudinal phase of the study, seven subjects failed to maintain an adequate training regime or refused to complete final laboratory testing. These drop-outs were evenly distributed over the long-term (1), de-training (2), postponed (1) and no-training groups (3). This left us with 55 subjects on whom the complete set of longitudinal measurements could be taken. The average time trained per week was 2.6 hours for the long-term group, 1.7 hours for the de-training and 1.5 hours for the post-poned group. No subject trained less than 1.1 hours a week. One-way ANOVA showed significant initial group differences in age ($F(3,51)=2.97$, $p< 0.05$), past sports behavior ($F(3,51)=3.91$, $p<0.01$) and daily bicycling ($F(3,51=4.71$, $p<0.006$). Before training, the no-training control group reported less past sports behavior than the other three groups. The long-term trainers were younger, and used a bicycle more often than the other groups. In spite of the differences in past and current physical activity habits, there were no initial group differences in either total energy expenditure or aerobic fitness.

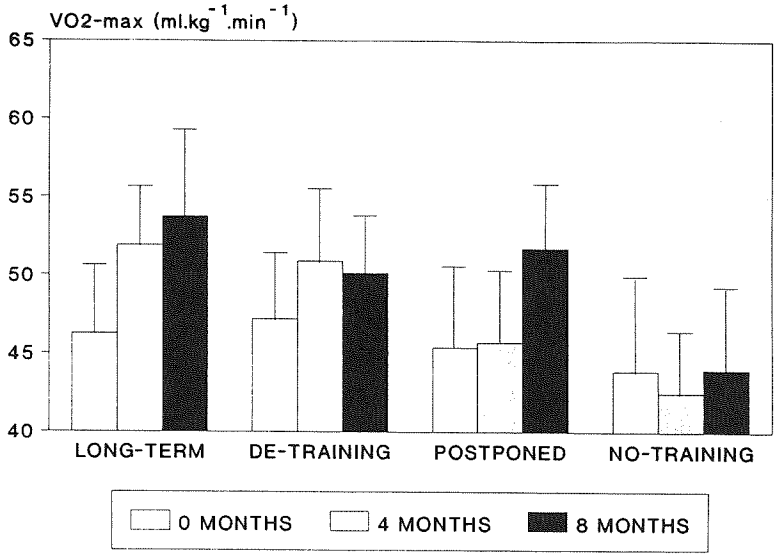

Figure 8: Training effects on the maximal oxygen consumption per kg body weight (Vo_2max).

The effects of the various training regimes on Vo_2max are displayed in figure 8. MANOVA yielded a significant Group by Months interaction ($F(6,100)=5.97$, $p<0.001$) for Vo_2max. Follow-up examination of the within-group effects showed that Vo_2max significantly increased in the long-term and de-training groups in response to the first four months of training. In the second four months period, an additional increase in

Vo_{2max} was seen in the long-term group, although this failed to reach significance. After de-training, Vo_{2max} was still significantly higher than the pre-training level, suggesting that some of the improvement in fitness was still present even after de-training. The postponed training group showed significant increases in Vo_{2max} only after they had taken up training in the second four months period of the study. No significant changes in Vo_{2max} were seen in the control group at any time. The ecological validity of the increase in Vo_{2max} was demonstrated by improved performance on a field endurance test. Four months of training reduced the average time needed to complete a 5 km run from 24 min 15 sec to 22 min 10 sec. After 8 months of training the long-term trainers were able to complete the 5 km run in the average time of 21 minutes and 30 seconds. In summary, joint evaluation of Vo_{2max} and run times supports the idea that cardiovascular fitness had been successfully manipulated according to group assignment.

Training effects on psychological make-up

Psychological make-up of the four groups showed only minimal differences at the start of the study. State anxiety ($F(3,51)=3.23$, $p<0.04$) and negative mood at work ($F(3,51)=3.41$, $p<0.03$)) showed a significant initial group difference, and post-hoc examination revealed that in both cases the long-term group was more anxious and reported more negative mood than the no-training group. To account for these initial group differences, repeated measurement analyses on these variables will use the scores from the first measurement as a covariate. The postponed and de-training groups were not discriminable from each other or the other two groups on any psychological dimension. All subjects estimated themselves to be of average or slightly below average fitness and the trainers generally expected to benefit "quite a lot" from the training program. In rating their fitness, subjects said to have looked predominantly at their own fitness level in the past and to a lesser degree at fitness of peers and colleagues. There were no initial group differences in self-rated fitness, and all three training groups had similarly high expectations regarding the physiological and psychological benefits from training. Furthermore, all groups indicated that they considered regular exercise more important than other pleasant past time activities for the general well-being of people.

In the course of the study, a significant Group x Months effect appeared on subjective fitness estimates ($F(6,100=6.20$, $p<0.001$), and the Perceived Physical Ability subscale of the Self Efficacy list ($F(6,100)=2.47$, $p<0.03$). After training subjects indicated to feel more physically fit than before training, and they also scored higher on the Perceived Physical Ability subscale of the Self Efficacy list. No effects were seen in the no-training group, and in the second four months period perceived physical ability decreased to pre-training level in the de-training group. The training-induced increase in subjective fitness ratings is not surprising, since subjects were well aware of their improved performance on the running track. However, in spite of the successful manipulations of both objective and subjective fitness level, and in spite of the extensive psychological assessment, we found no training effects on any of the other psychological variables measured. Repeated measurement MAN(C)OVAs of the questionnaires failed to yield the significant Group X Months interactions that could have been indicative of a training effect. In fact, not even

a main effect of Months was found within any of the groups, suggesting that the answers to the questionnaires were highly reliable over time. In conclusion therefore, the results contradicted our hypothesis that training would influence the psychological make-up.

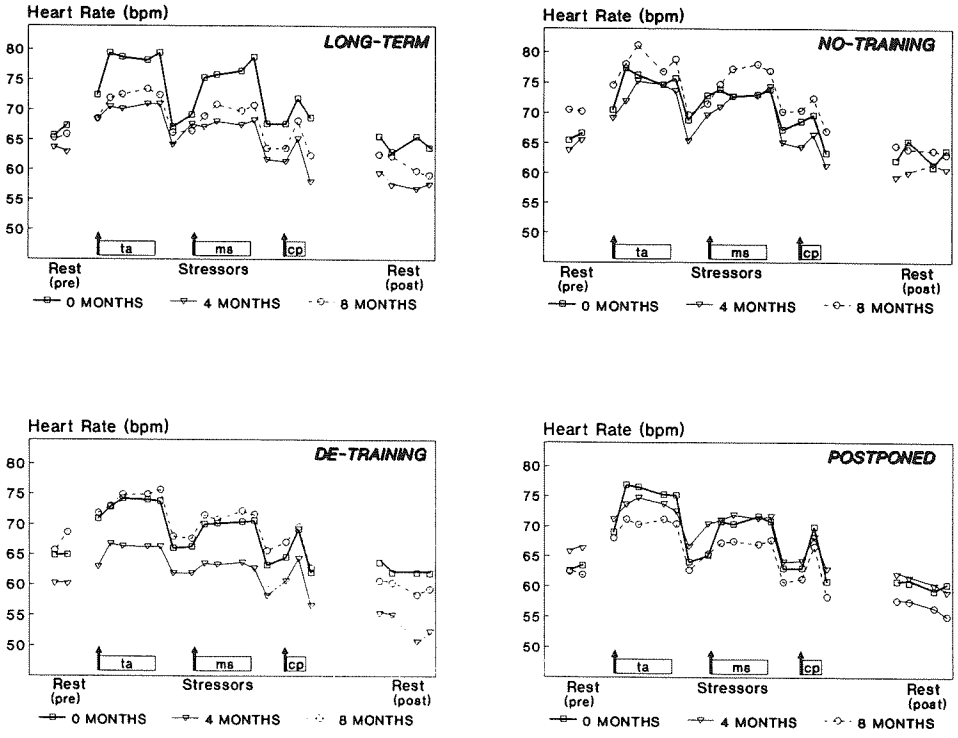

Figure 9: Training effects on the Heart Rate. The four panels give the Heart Rate during laboratory testing at 0, 4 and 8 months for each group separately.

Training effects on physiological reactivity

Figure 9 shows the HR levels during the several laboratory conditions at 0, 4 and 8 months. A Group(4) by Months(3) by Conditions(11) analysis of variance on the HR yielded a significant Conditions effect ($F(10,42)=36.4$, $p<0.001$) and a significant Group X Months interaction ($F(6,100)=3.18$, $p<0.007$). The HR responses seen during the first measurement, i.e. a significant increase above pre- and post-stress resting levels in anticipation to and during the three tasks, was replicated during the second and third

measurements, giving rise to the overall Conditions effect. There were no initial group differences in the HR response pattern, and there was no significant habituation of the HR reactivity to the stressors over time.

The Group X Months interaction was due a clear training effect on the HR. HR decreased in the long-term training group and remained decreased throughout the second training period. Training also decreased HR in the de-training group, whereas de-training completely reversed this effect. In the postponed training group, HR started to decrease only after training had begun. No systematic effects were seen in the no-training group. These patterns clearly point to a causal influence of training on the overall HR level. However, the absence of a Group X Months X Conditions interaction suggested that no single condition was specifically affected by training. Since changes in reactivity to one of the stressors might have been masked by the decrease in the overall HR level, we decided to re-examine reactivity to the three stressors after adjusting it for the decrease in the resting level. A Group X Months MANCOVA with the post-stress resting level as a time-varying covariate was used for this purpose. The MANCOVA yielded no effects of training on the adjusted reactivity to the stressors. Furthermore, additional inspection of the within-group effect in the long-term training group failed to show a significant reduction in HR reactivity, even after 8 months of intensive training. Therefore, we must conclude that training simply reduced the overall HR level, both at rest and during the stressful conditions, and no single condition was specifically affected.

Repeated measurements MANOVA on the SBP yielded a significant Months X Conditions effect only ($F(20,32)=4.2$, $p<0.001$). The SBP reactivity to the three stressors seen at the first measurement was replicated at the second and third measurement, i.e. the three tasks reliably increased systolic blood pressure. However, the amplitude of the responses to the reaction time tasks decreased from the first to the second session. Blood pressure reactivity to the tone avoidance and memory search tasks was reduced from 14.5 and 13 to 10 and 9.5 mmHg respectively. No reduction was seen in systolic blood pressure reactivity to the cold pressor test, and no further decreases in reactivity to the reaction time tasks were seen from the second to the third measurements. MANOVA of the PEP also yielded a significant Months X Conditions effect only ($F(20,32)=5.1$, $p<0.001$). From the first measurement to the second measurement PEP reactivity fell from -13 to -10 msec during the tone avoidance task and from -11 to -8 msec during the memory search task. In addition, resting PEP was significantly longer during the second measurement session. No further changes in PEP reactivity or resting PEP were seen from the second to the third measurement. The lengthening of the PEP at rest and the reduction of tasks-induced PEP and SBP responses probably reflect habituation to the tasks as well the laboratory environment itself. However, there were no significant interaction effects involving the Group X Months interaction for the SBP and the PEP, suggesting that there was no effect of the training manipulations on the overall level of these variables or their reactivity to any of the separate conditions.

MANOVA on the RR, RSA and RSA-red yielded only significant effects of Conditions. No significant effects involving Months or Group were found suggesting that reactivity of these variables did not change over time in any of the groups. Consequently, no evidence of a training effect on level or reactivity of these variables was found.

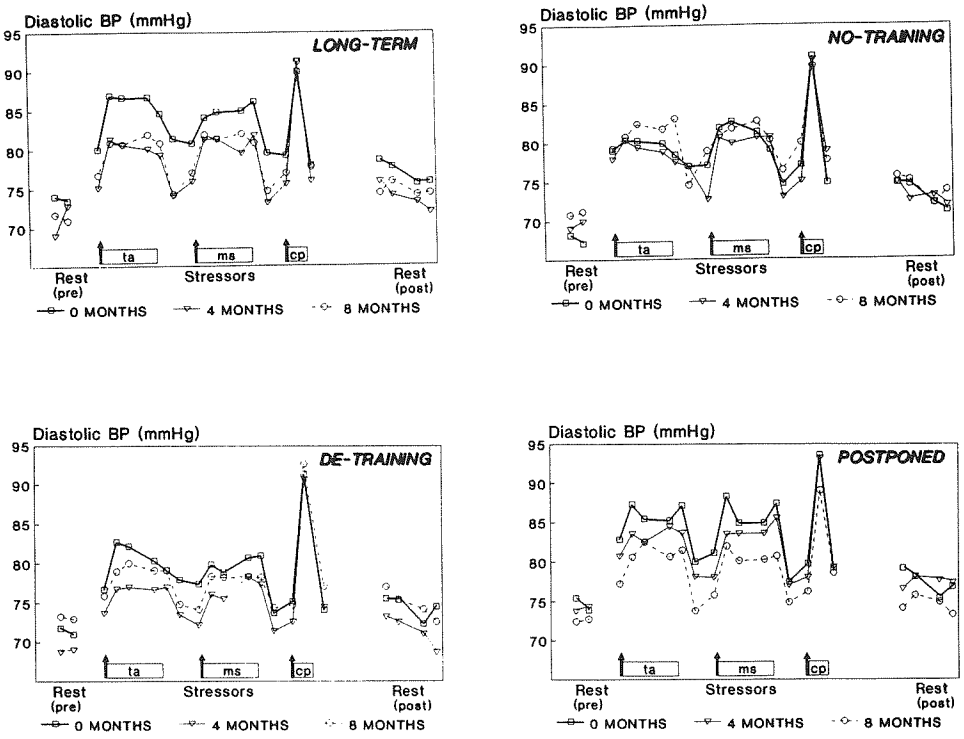

Figure 10: Training effects on the Diastolic Blood Pressure. The four panels give the Diastolic Blood Pressure during laboratory testing at 0, 4 and 8 months for each group separately.

Figure 10 shows the DBP level during all laboratory conditions at 0, 4 and 8 months. The Group(4) by Months(3) by Conditions(11) analysis of variance on the DBP yielded a significant Months X Conditions interaction ($F(20,32)= 2.47$, $p<0.011$) and a significant Group X Months interaction ($F(6,100)= 2.90$,$p<0.012$). The Months X Conditions interaction reflected a gradual decline in DBP response to the two reaction time tasks over the second and third measurements, with the response to the Cold Pressor test remaining unchanged. Within-group follow-up of the Group X Months interaction showed that the effect was caused by a reduction in DBP level after training. Four months of training reduced the DBP in the long-term training group and this reduction in blood pressure level was still present at eight months of training. No significant change over time was seen in the no-training group in any of the conditions. During the first 4 months of training, the overall DBP level decreased in both de-training and postponed

training groups. However, during the second months period DBP level shifted back upwards in the de-training group, whereas it decreased in the postponed training group, who had now taken up training. As with the HR, training did not specifically affect reactivity to the tasks or the anticipatory and recovery conditions, even after adjustment for the reduction in resting DBP. Instead, training reduced the overall level of DBP during all conditions.

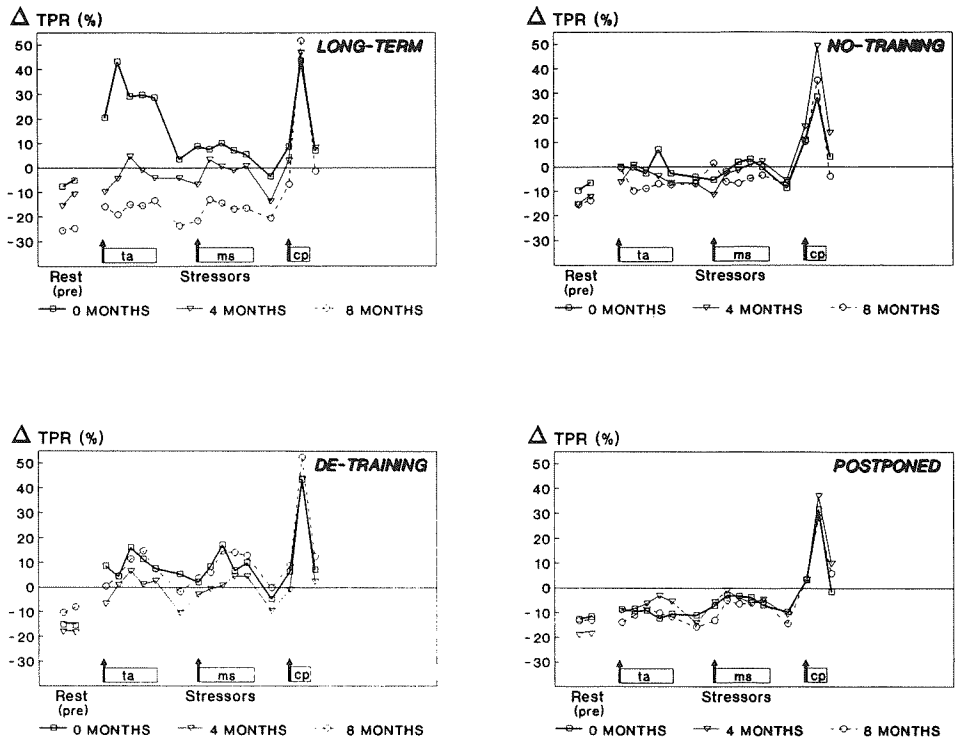

Figure 11: Training effects on the response of the Total Peripheral Resistance. The response of the Total Peripheral Resistance to the laboratory stressors at 0, 4 and 8 months is given for each of the four groups separately. The Total Peripheral Resistance response is given as a percentual change from the post-stress resting level.

Figure 11 gives the percentual change of the TPR from the post-stress level in response to the three stressors. There was a significant overall group difference in the TPR response to laboratory conditions ($F(27,113)=1.85$, $P<0.014$). At the start of the study, the long-term and de-training groups showed an increase in TPR above the post-

stress resting level during the tone avoidance and memory search tasks. In contrast, the postponed training group showed a decrease in TPR. TPR in the no-training group did not change from the post-stress level. To account for this initial group difference, the TPR reactivity at the first session was used as a covariate in the Group X Months X Conditions analysis. Only a trend toward a significant three-way interaction was found ($F(52,86)=1.30$, $p<0.13$). However, post-hoc examination of the within group effects showed a significant Months X Condition effect in the long-term training group. After the 8 months training program, the TPR response to the tone avoidance task was significantly reduced in the long-term training group. The strong increase in TPR, seen at the start of the study, was converted to a decrease in TPR by the end of training. A similar pattern was seen in the memory search task, although the within-group effect failed to reach the post-hoc significance level. In the long-term trainers, the CO response to the tone avoidance task followed exactly the opposite pattern from the TPR responses, i.e. it was seen to increase in the course of training. No significant changes over time were seen in the TPR or CO responses of the postponed training and no-training groups.

The pre- to post-stress increase in urinary adrenaline excretion seen during the first measurement was replicated during the second and third measurements, with no noticeable effects of habituation. However, no differential effects on adrenaline level or reactivity were noted for the four groups over time. No increase in urinary noradrenaline excretion after stress was found in any of the groups at any point in time.

Table 7: Performance measures and subjective estimates of effort and distress during the two reaction time tasks. Per group data are given for the first (0 months), second (4 months) and third (8 months) measurement.

	Long-term			**De-training**			**Postponed**			**No-training**		
	0	**4**	**8**	**0**	**4**	**8**	**0**	**4**	**8**	**0**	**4**	**8**
Tone Avoidance												
-RT (msec)	469.1	450.2	442.3	477.1	446.1	440.2	480.9	455.7	445.3	460.3	436.0	439.4
-Errors (%)	34.8	34.6	33.3	38.7	32.4	32.4	39.2	36.6	31.4	30.6	28.6	26.8
-Effort (pts)	73.4	80.0	74.0	63.4	71.8	63.2	72.3	79.1	69.4	60.7	67.1	65.5
-Distress (pts)	51.6	72.7	61.8	37.0	54.6	55.3	40.6	58.7	54.9	34.3	47.1	41.1
Memory Search												
-RT (msec)	777.2	699.2	670.5	817.8	725.5	673.2	816.3	740.8	703.0	772.6	688.3	689.2
-Errors (%)	13.6	12.7	10.7	16.3	11.9	13.5	11.3	12.4	11.0	13.2	15.5	12.0
-Effort (pts)	74.1	62.7	72.7	72.3	63.8	67.3	66.1	63.6	59.3	53.4	55.7	51.4
-Distress (pts)	43.0	43.2	54.5	40.5	56.3	43.3	36.1	38.5	39.7	35.7	29.3	38.1

Performance

Table 7 displays group data on performance indices and subjective indices of effort and distress. MANOVA yielded a significant effect of Months on the amount of errors made during the tone avoidance ($F(2,50)=285.3$, $p<0.000$) and memory search ($F(2,50)=180.1$, $p<0.000$) tasks, which was due to a gradual reduction in errors at repeated confrontation with the tasks. Further evidence for improved task performance over time is provided by the significant reduction in average reaction time

($F_{TA}(2,50)=7303.0$, $p<0.000$) ; $F_{MS}(2,50)=1744.2$, $p<0.000$). There were no significant group effects and training was not seen to enhance either speed or accuracy of reaction time task performance. The overall improvement in performance took place in spite of the fact that the tasks were made more difficult on repeated testing. Apparently, the increased task difficulty was offset by the effect of learning. Nonetheless, significant effects of Months were seen on subjective distress that increased over repeated testing (TA: $F(2,50)=5.96$, $p<0.005$; MS: $F(2,50)=5.01$, $p<0.01$). This suggests that our manipulation of task difficulty did result in a more stressful task. The important point to make however, is that no significant group differences in subjective distress were noted. Consequently, the lack of training effects on reactivity cannot be attributed to higher effort, higher distress, or better performance in the trained subjects.

Interdependency of training effects

Although, at a group level, little effects of training were found on psychological make-up and reactivity, there still existed the possibility that selected subjects did benefit from training, e.g. those who had gained most in Vo_{2max}, or those who had low initial fitness levels at the start of the study. To test this possibility, separate analyses were performed on the 44 subjects that received training at one time or another. Pre- to post training measurements over a four month period were pooled for the long-term, de-training and postponed training groups. Since we had deliberately allowed the training frequency to vary from 1.5 to 3.5 hours a week among our subjects, there was a substantial variation in training dose (number of hours trained). Furthermore, the correlation between the number of hours trained and the change in Vo_{2max} was only meager ($r=0.37$, $p<0.06$) and the variation in training effect (increase in Vo_{2max}) was substantial. Effects of initial fitness, training dose and training effect on the final training outcome were tested by directly correlating them to the pre- to post changes in reactivity and psychological make-up. Of these correlations, none was significant.

In a final analysis we tested the possibility that beneficial effects of training had been limited to subjects with the least favorable psychological profile at the outset of the study. Pre- to post training changes in questionnaire scores and reactivity were brought into relationship with the initial levels of neuroticism, negative mood and self-esteem. Increases in positive mood at work ($r = -0.40$) and self-esteem ($r = -0.47$) during the training period were inversely related to the initial level of these variables. Neuroticism was associated with a greater fall in trait anxiety ($r = -0.39$) and negative mood at rest ($r = -0.55$) in the course of training. However, these psychological improvements in selected subjects were not coupled to a simultaneous decrease in physiological reactivity.

Discussion

The present study sought to demonstrate an effect of regular exercise on the susceptibility to psychological stress, with aerobic fitness as the main intervening variable. Susceptibility to stress was indexed by a set of psychological variables that may influence frequency and duration of physiological arousal in real-life situations, and by measurement

of the amplitude and pattern of physiological reactivity to standardized laboratory stressors. A combined cross-sectional and longitudinal approach was used to relate (changes in) fitness to (changes in) psychological make-up and physiological reactivity. In spite of the innate complexity of the questions posed, the results were straightforward. Contrary to our hypothesis, aerobic fitness was not associated with a favorable psychological profile, and the fit subjects were high, rather than low stress-reactors. No effects of exercise training were found on psychological make-up even if intensive training was continued for 8 months. Beneficial effects of regular exercise were limited to the reduction in the overall level of heart rate and blood pressure under stress, and the attenuation of the initially high peripheral resistance response in the long-term training group. No effects were found on heart rate or blood pressure reactivity, nor on urinary catecholamine excretion or cardiac β-adrenergic drive. These results are difficult to reconcile with previous suggestions of reduced susceptibility to psychological stress after chronic exercise.[254, 62] Furthermore, the higher blood pressure reactivity in the more fit subjects contrasts with the general view on reactivity as an "unhealthy" trait. In the remainder of the discussion we will explore the causality of the relationship between exercise behavior and psychological make-up, and present an alternative view on the link between fitness, reactivity and disease.

Recent large-scale population studies have reported a favorable psychological profile in people with high levels of leisure time physical activity.[548, 478] Because many people motivate their exercise habits by the sheer fact that it helps them to relax[548] , this cross-sectional relationship at first sight suggests that regular exercise has a beneficial influence on psychological functioning, in particular on mood and well-being. The results of the present study do not support this contention. We found no effect on indices of anxiety, depression, or hostility, and training did not influence type-A behavior, anger-handling or any other coping style. Furthermore, neither negative nor positive mood at work were altered in response to training, and previous reports of increased self-esteem[244, 245, 536] and self-efficacy[350, 351] after training were not replicated in the present study.

It is possible that the lack of profound psychological training effects in our study was due to some shortcomings in its methodology. Only subjects in the de-training and postponed training groups had been randomly assigned. Grouping of subjects in the long-term and no-training group had been based on self-selection for both practical and ethical reasons (it would be very unpleasant to apply for 8 months of training and then find you were to remain untrained for an additional 8 months period). However, the failure to find training effects is not likely related to this self-selection. Long-term trainers appeared to have a less favorable psychological profile at the start of the study, which should have enhanced, rather than decreased chances of improvement.[405, 608] In addition, their voluntary participation in long-term training may reflect a greater expectancy of psychological benefits. Again this should increase, rather than decrease the chances of finding improved psychological make-up in this group. A second flaw in the present study might be the absence of an alternative treatment group, e.g. strength/flexibility training or an attention-control condition. Had training effects occurred, then subjective expectancy and non-exercise related (social) attention effects

might have been responsible, rather than the aerobic exercise per se. Clearly, this interpretative problem never arose, since we did not find any changes in psychological make-up in the course of training.

Perhaps, the average increase in fitness in the present study was not large enough to induce psychological benefits. Evidence for a direct connection between aerobic fitness and psychological functioning comes from cross-sectional studies showing a weak but significant link between various fitness indices and psychological characteristics, like depression, emotional stability, extraversion, anger, self-confidence and social adjustment.[270, 348, 349, 248, 102, 69] Unfortunately, exercise behavior and fitness in these studies partly overlapped, and it is unclear which of them was (weakly) associated with a favorable psychological make-up. In the present study we deliberately used a group of subjects with a relatively homogeneous activity status, to prevent the confounding effects of exercise habits. Although substantial individual differences in Vo_{2max} were found, probably related to constitutional differences, no significant relation with any of the psychological variables was found. Furthermore, we did not find psychological training effects in selected group of subjects who 1) had low initial fitness levels, 2) trained intensively for 8 months, or 3) had large training-induced increases in Vo_{2max} (up to 42%). Several other studies have failed to report psychological effects too, in spite of clear increases in fitness.[302, 338, 411] Within the studies that do find a psychological effect of training, there is often no direct relationship between the amount of fitness change and the changes in the psychological variables.[521, 151, 210, 553, 425] Finally, Cramer et al.[98] recently reported an increase in well-being after 15 weeks of brisk walking, although no significant change in Vo_{2max} took place. When we combine these findings, the conclusion must be that a change in fitness may not be a necessary, and is certainly not a sufficient condition for a change in psychological make-up to take place.

Although the results of our study contrast with that of others,[521, 25, 98, 274, 388, 480, 363, 553, 210] it is in agreement with a growing number of studies that do not find any psychological effects of exercise training.[263, 523, 477, 302, 411, 338, 2] What could explain the different outcome of these studies? The choice of subjects seems an important factor. Many of the studies reporting beneficial psychological effects of exercise, have used extreme populations, like high anxious[553, 350] , depressed[388] , highly stressed[480] , or delinquent subjects[245, 363] , and even in "normals" the training-induced changes in mood[521] , anxiety[608] , depression[405] , type-A[274] , or self-esteem[244] are generally found to be largest in the subjects with the least favorable psychological profile before the start of the training. Correlation of the changes in depression on the initial level was found to be as high as +0.89.[480] Furthermore, several studies suggest that the advantages of fitness training only start to show up when "the going gets tough", i.e. when subjects report a large amount of life stress.[253, 62, 63] Perhaps, the subjects in the present study were simply too "normal" to allow a psychological effects of training. They were all healthy working males, most of which had been active in recreative or competitive sports before, but through changes in work or family life had drifted to a sedentary lifestyle over the past years. As a group they reported little psychological problems and normal levels of self-esteem. Mood did not deteriorate from weekend to workdays, and average scores for both positive and negative

mood were within the normal range. Only when subjects with a low initial level of self-esteem and a high initial level of negative mood were used some training-induced improvement in anxiety and self-esteem was seen.

In short, beneficial psychological effects of exercise may be limited to subjects who experience (severe?) psychological disturbances before the start of training. These subjects may account for the findings of two major prospective studies on the association of physical activity habits and mental health, which found recreational physical activity to be a significant predictor of depressive symptoms later in life.[163, 73] However, the association between well-being and physical activity in a large population survey still held when the 13% most depressed or anxious persons were eliminated from the analyses.[478] Since little psychological training effects could be detected in "normal" subjects, this means that, in the population at large, the favorable psychological profile of regular exercisers must partly reflect self-selection. Self-selection might have been based on individual differences in endowment for aerobic fitness, but our data suggest that fitness is not a crucial factor in psychological functioning. Thus, the selection must be of a psychosocial nature, i.e. emotionally well-adjusted, agreeable and self-confident persons are more attracted to sports and exercise and have the energy and self-discipline to maintain that behavior over the years. Consequently, a favorable psychological profile may be a cause of individual differences in exercise status, rather than vice versa.

The lack of training effects on in heart rate or blood pressure reactivity was less surprising than the failure to find changes in psychological make-up. In several previous studies, measuring heart rate and blood pressure reactivity before and after 8 to 12 weeks of training[523, 477, 255, 38, 511, 40, 554, 89] , only the initially low fit female students of Holmes & McGilley[255] reported significantly lower heart rate reactions after training. Training-related reduction in blood pressure reactivity was found only by Sherwood et al.[511] , and the effect was limited to a subset of 5 borderline hypertensives. Previously, a greater increase in urinary catecholamine secretion was reported in trained subjects[113] , but this was not supported in the present study. Likewise, plasma catecholamine reactivity is not changed after training.[113] , but this was not supported in the present study. Likewise, plasma catecholamine reactivity is not changed after training.[524, 40, 89] The absence of a training effect on the recovery to our tasks also replicates the findings of others[523, 477, 554, 40] , although one study did report faster recovery of heart rate and blood pressure levels after aerobic training.[38] Together with the meager results of these previous studies, our results strongly argue against a causal influence of training on heart rate, catecholamine, and blood pressure reactivity, even if aerobic fitness is increased.

In contrast to the heart rate, catecholamine and blood pressure responses, shifts in cardiac output and vascular resistance have been much less studied. In the present study, the only notable exception to the absence of training effects on reactivity was a reduced rise in the total peripheral resistance in the long-term training group, coupled to an increase in the cardiac output response. The decrease in TPR response is in agreement with the known increase in vasodilatory effects of adrenaline in the well-trained[564] and athletes have been shown to have reduced TPR response to stress in comparison to sedentaries.[130] Since stroke volume is known to increase after training, an unchanged

heart rate reactivity must give rise to a higher cardiac output response, unless the stroke volume response to stress is much smaller after training. No decrease in stroke volume or contractility was seen in the present study, and the cardiac output response was indeed increased by training. Our data contrast with two other studies that have found increased TPR and reduced cardiac output responsiveness after aerobic training.[511, 89] The use of absolute impedance-derived stroke volume, rather than change scores, may explain part of the differences. More likely the strong increase in TPR to the tone avoidance task in the long-term group was a prerequisite for the decrease in time to occur. Together with the lack of TPR effects in the de-training and postponed groups this may mean that the effect simply reflects habituation or regression toward the mean, rather than being related to training. On the other hand, reduction of TPR responsiveness in subjects with a strong vascular response to stress may be a reliable phenomenon, deserving further study. That the subgroup of vascular reactors self-selected to participate in long-term training is unfortunate, but intriguing

The absence of training effects on cardiovascular reactivity, in spite of a clear cut improvement in fitness, contrasts with the cross-sectional findings of lower reactivity in high fit exercisers. About half of the many studies comparing physiological stress-responses of high fit with that of low fit subjects have reported lower reactivity[254, 343, 584, 130, 352, 102] or faster recovery in the high fit.[60] Unfortunately, the fitness level in most studies was completely confounded with exercise habits, since the high and low fitness groups were selected on the basis of their current participation in sports (e.g. athletes vs sedentaries). In the previous chapter, direct correlation of Vo_{2max} with reactivity had shown lower diastolic blood pressure reactions in the more fit subjects in combination with enhanced cardiac vagal control. Although virtually the same experimental design was used in the present study, the results were completely different. No relation was found between fitness and the RSA decrease during stress, and the more fit subjects showed high, rather than low blood pressure reactivity. There was only one apparent difference with the previous study. The tasks were more challenging and distressing because of the very competitive task structure and the high ego-threat following from the team responsibility. Under these conditions fitness appears to be associated with high, rather than low reactivity. Similar results had been reported before by Lake et al.[324] High fit subjects had significantly lower blood pressure reactivity to a Structured Interview, but during competitive card games with harassment high fit type-A's had stronger diastolic and mean arterial blood pressure reactions than their sedentary counterparts or type B's. Although no explicit mention of higher reactivity in fit subjects was made in any other study, many authors have used covariance analyses, acting on the rationale that the lower levels in the high fit may give rise to higher reactivity (e.g. Czajkowski et al.[102]). Apparently, the idea that high reactivity and low basal levels are a natural consequence of fitness is not unique to the present study.

The association of fitness with high blood pressure reactivity is intriguing, since it contrasts with current psychosomatic theorizing, that considers high reactivity to be a risk indicator for cardiovascular disease. Within the field of psychosomatic medicine the concept of a "high stress-reactor" has become as prominent as the concept of "disease-prone personality", of which type-A is the most cited example. It is intuitively appealing

to link the two concepts, i.e. to consider the disease-prone individuals to be the ones with exaggerated physiological responses to situational challenges. Many elegant psychosomatic theories have been devised to explain how physiological hyperreactivity may render the high-reactors more susceptible to stress-induced disease.[372, 385] Unfortunately, studies prospectively linking stress-reactivity to disease are scarce.[371, 374] In post-infarction patients, low heart rate reactivity to a video game appeared to be predictive of cardiac arrest, rather than high reactivity.[3, 182] The only study predicting future mortality in healthy humans from high blood pressure reactivity used the cold pressor test, rather than a psychological stressor.[300] An additional problem is that individual responses towards real-life stressors correspond only moderately to laboratory responses, suggesting that laboratory tasks may not reflect real life stressors very well.[132] Hoever, even the coupling of real life stressors to high reactivity has been directly challenged by Siegrist et al.[518] , who found that chronic occupational stress was associated with reduced cardiovascular responsiveness to a standard mental test at the end of a working day.

The finding of high reactivity in the more fit subjects of the present study presents yet another anomaly to a rigid reactivity-disease paradigm. In contrast to reactivity, aerobic fitness has proven itself to be inversely associated with the risk for cardiovascular disease in large epidemiological trials.[147, 35] Comparison of high to low fit quartiles suggests a 4.8 to 8.5 fold risk for cardiovascular disease death in the low fit. With such figures it is difficult to envisage that the higher blood pressure reactivity in our more fit subjects are predictive of later disease. Furthermore, the unchanged reactivity after taking up exercise, a manipulation widely held to lower CHD risk, does not support a crucial role of stress-reactivity in CHD either. Most of these interpretive problems largely disappear when we cease to look at reactivity per se, but concentrate on the stress **levels** instead. In spite of high blood pressure reactivity, we found fitness to be associated with lower levels of heart rate and blood pressure at rest and during recovery at all three measurements independent of training state. This is in agreement with virtually all cross-sectional studies where the overall level, including the stress level, of these parameters was consistently lower in the high fit.[265, 252, 538, 102, 352] The lack of training effects on acute stress-reactivity in our study was paired to a significant lowering of the overall levels of heart rate and blood pressure, including the levels during stress. The reduction in heart rate level during the stressors was also found in virtually all of the other training studies[523, 477, 255, 38, 511, 40, 554] , and two other studies have reported decreases in diastolic blood pressure under stress.[40, 511] Furthermore, our findings are in good agreement with most cross-sectional studies showing people who exercise regularly have systematically lower heart rate and blood pressure levels under stress than non-exercisers.[324, 255, 343, 130, 352, 102, 89]

At first sight these findings seem trivial. They support the claims of exercise physiologists that regular exercise is beneficial for health by reducing basal blood pressure and heart rate, but do not seem to add extra information from a stress point of view. However, the continuation of lower levels of heart rate and blood pressure when the trained subjects transgress from rest into stress is an important extra finding. Most of our waking time is not spent at rest but under light mental and emotional strain, the effects of

which on heart rate and blood pressure normally peak at the work situation.[232, 268, 583] Average daily levels of cardiovascular activation may be much more relevant to later disease than resting levels. Evidence supporting this comes from studies that have shown blood pressure during habitual daily activity to be a better predictor for the incidence of cardiovascular complications than pressure at rest.[449, 369] Similarly, the association of current target organ damage is significantly better[533, 110, 607] with ambulatory blood pressure than with casual or clinic pressure. Accordingly, we hypothesize that, even if training failed to change acute task-induced reactivity, it may still reduce the **impact** of stress on health, by reducing the overall levels heart rate and blood pressure.

In summary, the present study suggests that in a normal population, psychological make-up is not influenced by exercise training, and aerobic fitness is not a biological correlate of personality. In further contrast to our hypotheses, aerobic fitness was associated with higher cardiovascular reactivity to mental stress, whereas training, even of 8 months duration, had no effects on stress-reactivity. However, the lack of training effects on cardiovascular stress-reactivity was amply compensated by the overall lower levels of heart rate and diastolic blood pressure seen after training. These physiological adaptations must account for the well-known protection against heart disease, particularly if they coincide with other hypothesized effects of exercise, like a lower LDL/HDL cholesterol ratio, lower body fat, increased insulin-sensitivity and increased fibrinolytic potential. Psychological or psychophysiological factors do not seem to contribute, at least not in psychologically normal middle-aged males. The present study leaves completely unchallenged the ideas that stress is "bad for the heart" whereas exercise is "good for the heart". It does suggest however, that there is no direct interaction between the two, i.e. that stress and exercise exert their opposite effects on our health independently.

7. Effects of fitness training on plasminogen activator inhibitor activity: relationship to changes in cardiovascular fitness, body composition and the lipid profile.

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Introduction

Regular exercise has been demonstrated to effectively reduce the incidence of non-fatal and fatal coronary heart disease (CHD).[459] However, the precise mechanisms behind this effect are still unclear. Controlling for the major CHD risk factors (smoking, cholesterol, blood pressure) still leaves a substantial part of the protective effect unexplained.[436, 126, 492] With increasing evidence that the interaction of the vascular endothelium with blood plays a crucial role in the pathogenesis of vascular disease[231, 215, 281, 472, 432, 415] the need for exploring the effects of regular exercise on the coagulation/fibrinolysis balance has expanded. Various studies, examining the acute effects of a bout of exercise, have demonstrated a clear increase in fibrinolytic activity following strenuous exercise, as indicated by decreased euglobulin lysis time, increased fibrinogen degradation products and increased release of plasminogen activators from the vascular endothelium (reviewed in Bourey & Santoro).[52] In parallel to the increase in fibrinolysis, many studies have demonstrated increased coagulability after acute exercise, that appears to be due to the action of both the soluble coagulation system[266, 169] and the platelets.[104, 136] It is at present not known to what extent the increased fibrinolytic potential during physical exercise counteracts this concomitant increase in the coagulation. Appreciable conversion of fibrinogen to fibrin and the release of fibrinogen degradation products may occur only at high intensity exercise (80-90% of maximal capacity), or after prolonged periods of exercise.[104, 138, 353, 148] In addition, the specific effects of exercise training on the fibrinolytic response have been inconsistent. Increased fibrinolytic responsiveness has occasionally been reported[169] , but generally no effects of training were found.[168, 138, 495, 258]

When considering the preventive effect of regular exercise on vascular disease, the change in the dynamic equilibrium between coagulation and fibrinolysis during acute exercise may not be the crucial issue. Instead the long-term adjustment of the fibrinolytic system under non-exercise conditions may be more relevant, particularly of those components that are thought to convey a health risk. One of these components is plasminogen activator inhibitor-1 (PAI-1). PAI activity in blood samples has recently been shown to be a risk indicator for venous and arterial thrombosis.[231, 215, 281, 472, 432, 415] PAI plays an important role in fibrinolysis by its inhibitory binding to tissue plasminogen activators (tPA and u-PA). The latter, by converting plasminogen to plasmin, forms the crucial step in the fibrinolytic pathway. Elevated PAI activity may disrupt the fragile balance between PAI and the plasminogen activators, thus facilitating deposition of fibrin on the vessel wall. Prospectively, high PAI activity indeed precedes atherosclerotic complications, although a causal relation is as yet unproven.[234] If the protective effect of

regular exercise is in part due to effects on the clotting/fibrinolytic balance, then training may well be expected to lead to decreases in this important risk indicator.

Cross-sectionally, a relation between physical activity status and PAI activity has indeed been demonstrated. Young athletes had lower PAI values than age-matched sedentaries, and elder sportsmen had lower PAI values compared to patients that suffered from myocardial ischaemia (MI).[541] However, it is unclear whether this relationship depended on constitutional or pathology-related differences between the trained and untrained groups, or whether low PAI activity was truly induced by training. There are at present only three longitudinal studies known to us that tried to delineate the causal effects of training on PAI activity.[154, 219, 559] Comparison of cardiac rehabilitation programs with and without exercise showed that there was a steady increase in PAI activity in the non-exercise group over time, whereas PAI activity in the trained group remained constant.[154] Although training did not truly decrease PAI activity, the authors suggested that it prevented the normal deterioration of fibrinolysis as seen in untrained patients. In a second study, three months of aerobic fitness training, combined with smoking cessation, substantially reduced PAI levels in healthy young subjects. This reduction was maintained during 3 subsequent months of low intensity training even if subjects took up smoking again.[219] A final study, comparing PAI activity before and after 6 months of intensive training, revealed a significant decrease in PAI activity, although this training effect was limited to older subjects.[559] Unfortunately, the latter two studies used no control groups, so seasonal effects could not be ruled out. The first aim of the present study was to test the effects of aerobic fitness training on PAI activity, using a more extensive experimental design.

Several mechanism can be identified that could underly a training-induced reduction in PAI activity. Reduced PAI activity could be related to the changes in cardiovascular fitness known to result from training, e.g. the increase in maximal oxygen consumption (Vo_{2max}) or the decrease in resting heart rate and blood pressure.[621] More likely however, fibrinolytic effects would be related to changes in body weight and body fat,[55] accompanying the increase in fitness, or the lower levels of triglyceride and low density cholesterol (LDL-C), and the relatively high levels of high density cholesterol (HDL-C) seen in regular exercisers.[616] Body composition has shown a clear cross-sectional relationship with PAI activity, both in normal and obese subjects[589] and in particular dominance of peripheral fat over central fat may be associated with lower PAI activity.[326] Longitudinally, reduction of body fat through dieting has shown to result in lower PAI activity.[264] In addition, there is a known connection between hyperlipoproteinaemia and/or hypertriglyceridaemia and reduced fibrinolytic capacity, and lipid lowering diets as well as cholestyramine may increase fibrinolytic capacity by decreasing PAI.[11, 307] In vitro studies have confirmed the potential of HDL-C, LDL-C, and triglycerides to stimulate PAI activity.[418, 557] In vivo, particularly very low density lipoprotein cholesterol (VLDL-C) and triglycerides have been found to be related to PAI activity,[230, 394, 17] perhaps because they cause the release of PAI-1 from the endothelium.[418] Apart from elucidating the effects of aerobic exercise training on resting PAI activity, the present study aimed at relating the training-induced changes in PAI activity to changes in cardiovascular fitness, body weight, body composition, and the

lipid profile.

Methods

Subjects and training group design

Measurements were performed on the same 55 subjects used in the previous chapter, but blood samples from 5 subjects (3 de-training, 2 postponed) were lost or considered unusable because subjects had failed to meet the requirements of an overnight fast. This left us with 50 subjects on whom the complete set of longitudinal measurements could be taken. Training groups design and training programs were as detailed before (chapter 6).

Blood sampling

Blood was collected after three minutes of quiet sitting in a recliner chair in the physician's office. Before they were called in, subjects had been seated in the waiting-room for an additional 10 to 20 minutes. Subjects were required to refrain from eating breakfast and to abstain from smoking and drinking either coffee or tea on the morning of the venipuncture. In addition, they refrained from alcohol usage during the previous night. Since there are strong circadian fluctuations in PAI activity, blood samples were all taken in the morning between 9.00 and 11.00 hours. Furthermore, during the repeated intra-individual measurements at 4 and 8 months we strove to measure each subject at exactly the same time as was done at the first measurement at month 0. For several subjects this did not succeed, leading to a maximal time difference of up to 1 hour, e.g. venipuncture could be performed at 9.10 during the first measurement, at 10.10 during the second measurement and at 9.20 during the last measurement. Two subjects were shift-workers, which may have resulted in a possible phase difference in their circadian rhythm. Since the analyses in this study were predominantly intra-individual and they were on the same shift at all three measurements, these subjects were not removed. Post-training blood sampling was done between 2 and 8 days after the last training session.

Handling of blood samples and biochemical assays

Blood (9 vol) sampled for determination of PAI activity was collected in siliconized tubes on citrate (1 vol) containing prostaglandin E2 and theofylline (final concentrations 0.09 μM and 1 mM, respectively), placed on ice and centrifuged (20 minutes 2500xg) within 10 minutes at 4oC to obtain platelet poor plasma (PPP). Aliquots of PPP were snap frozen and stored at -70^{o}C until processing. Blood samples for lipid determinations were collected in tubes without anticoagulant, and were let to clot at room temperature for 30-60 minutes. The tubes were then spun at 3000 xg and the serum aspirated after which it was stored at -80^{o}C until lipid analyses took place. Plasma plasminogen activator inhibitor activity was determined by titration with purified two chain t-PA (Organon Teknika, Turnhout, Belgium) using a parabolic rate assay, as previously described.[592]

Values are expressed in percentage of a pooled plasma standard (290385) determined to neutralize 7.6 IU/ml of t-PA activity. Total serum cholesterol and HDL-C were determined by the enzymatic CHOD-PAP method (Boehringer, CAT 236691). HDL-C was determined in the supernatant after precipitation of VLDL-C and LDL-C with MnCl2 and natriumphosphowolframaat.[594] LDL-C was calculated using the Friedewald formula.[195] An extra variable was added to this set by taking the ratio of LDL-C and HDL-C (LD/HD Ratio). Serum triglycerides were determined by the enzymatic GPO-PAP method, using the commercial kit of Boehringer (CAT 701904).

Laboratory testing

Blood pressure, heart rate, and Vo_{2max} were measured as detailed in the previous chapter. From the height and weight, body mass index was computed as: BMI = weight/height^2. Body fat was determined as the sum of skinfold thickness at four locations: biceps, triceps, subscapula, supra-iliaca. This sum was converted to percentage body fat according to Durnin & Rahaman.[139] The ratio between the skinfolds taken from the trunk and the brachial skinfolds was used as an index of central to peripheral body fat (CP Fat Ratio). Estimates of body fat percentage from skinfolds have previously been shown sensitive to short-term training effects.[337]

Although subjects were not asked to change other habits than their exercise behavior, possible changes in other lifestyle variables could not be ruled out beforehand. Therefore, subjects were asked to fill out questionnaires about their smoking habits (average no. of cigarettes smoked daily) and they also self-reported the amount of coffee they drank (cups per day) and their average daily alcohol consumption (beer in a beer glass, wine in a wine glass, etc.).

Data analysis

To outline the possible effects of training, all variables were submitted to analyses of variance with training groups (4) as a between subjects factor and months (3) as a repeated measurement factor. The MANOVA option of the SPSS/PC+ statistical software package was used for this purpose. Before multivariate testing, normality of the variates was ascertained by inspection of the Boxplots and the Cochrans statistic and homogeneity of variance was tested with Box's M. Significant Group X Months interactions were followed-up to test whether group differences occurred over the first or the second four months period. Simple effects of months were tested within each of the four groups to delineate the effect of each individual treatment.

Differences between pre- and post training measurements were pooled over the three groups that received 4 months of training at one time or another during this study (long-term and de-training: 0 to 4 month; postponed: 4 to 8 month). This procedure yielded training-induced changes in PAI activity, cardiovascular fitness, body composition and lipids for 38 subjects. Thus, training-induced changes in PAI activity could be correlated with the corresponding changes in cardiovascular fitness, body composition, and the lipid profile.

Results

Table 8 gives the per group descriptives on all variables as measured at the start of the study.

Table 8: Per group means and standard deviations of the antropometric, cardiorespiratory, hematologic, and lifestyle variables. The descriptives were computed using data from the first measurement at the start of the study (0 months).

	long-term (N=10)		de-training (N=14)		postponed (N=14)		no-training (N=9)	
Age (yr)	32.1	±4.6	31.2	±3.5	33.5	±4.3	35.0	±3.5
Heigth (cm)	180.6	±5.6	183.7	±3.8	184.6	±4.9	182.1	±6.1
Weight (kg)	74.9	±7.6	77.0	±6.0	78.7	±6.6	75.4	±9.5
Body Fat (%)	18.6	±3.75	17.7	±3.9	18.9	±2.5	19.0	±3.1
CP Fat Ratio	2.24	±0.43	2.23	±0.74	2.18	±0.39	1.95	±0.62
VO_{2max} ($ml.kg^{-1}.min^{-1}$)	46.6	±5.9	47.6	±5.9	45.4	±6.9	43.6	±5.8
Heart Rate (bpm)	64.4	±9.5	62.0	±10.0	60.2	±6.8	61.0	±9.6
Systolic BP (mmHg)	127.1	±6.3	124.8	±11.0	124.1	±8.9	120.7	±7.4
Diastolic BP (mmHg)	77.5	±4.4	75.7	±8.1	77.3	±7.8	73.2	±6.2
TC ($mmol.l^{-1}$)	4.89	±0.87	4.89	±1.44	4.58	±0.88	4.47	±1.07
LDL-C ($mmol.l^{-1}$)	3.25	±0.70	3.15	±1.20	2.83	±0.67	2.93	±0.96
HDL-C ($mmol.l^{-1}$)	1.22	±0.28	1.23	±0.21	1.19	±0.24	1.06	±0.13
LDL/HDL Ratio	2.71	±0.0	2.62	±0.0	2.43	±0.0	2.84	±0.0
Triglycerides ($mmol.l^{-1}$)	0.93	±0.23	1.09	±0.53	1.12	±0.67	1.08	±0.42
PAI activity(%)*	93.9	±37.9	134.8	±66.8	61.9	±25.6	88.6	±70.4
Smokers (cig./day)**	2	(9.6)	3	(17.5)	4	(14.5)	3	(25.0)
Coffee (cups/day)	5.0	±2.4	5.7	±1.8	5.1	±1.7	6.1	±2.0
Alcohol (gl./day)	1.1	±1.6	1.6	±1.4	0.92	±1.0	2.1	±1.6

*) PAI activity was assayed according to Verheijen et al.[592] and is expressed in a percentage relative to a pooled plasma standard.

**) The number of smokers in each group is given, with the average number of cigarettes smoked in parentheses.

Height, weight and percentage body fat show that in general these were non-obese subjects. One subject was found to have familial hypercholesteraemia, with LDL-C values larger than 7.0 mmol/l (269 mg/dl) and two subjects showed consistent hypertensive blood pressure readings (>140/90 mmHg) during laboratory testing. Data from these subjects (one from the long-term training group, two from the postponed training group) were removed from the descriptives in table 8 and all further analyses. The resulting subjects were therefore non-obese normotensives with a cholesterol profile that was within the normal range for Dutch males.[313] There was a large spread of PAI activity both within and between groups and normal distribution was attained only after logarithmic transformation. The log transformed PAI activity will be used in all further analyses. Average PAI activity of all subjects, combining all four groups, was 97 % of the pooled plasma standard, which suggests that this population had fairly average PAI activity. However, there was a significant between-group difference in initial PAI activity ($F(3,44)=5.6, p < 0.01$). Post hoc testing with Tukey HSD showed that initial PAI activity in the de-training group was significantly higher than PAI in the postponed group. Since assignment to these groups was random, the difference most likely reflects a chance effect. However, because of these initial group differences, subsequent training effects on

PAI activity will be tested with MANCOVA using PAI activity at the first measurement as a covariate. No significant initial group differences were observed for any of the other variables.

Table 9: Relationship of PAI activity to anthropometric, cardiovascular, metabolic, and lifestyle variables. Correlation coefficients were computed separately for measurements at 0, 4 and 8 months into the study, combining the data from all subjects. These correlations are therefore uncorrected for training status.

	PAI activity (%)		
	0 month	**4 month**	**8 month**
Age (yr)	-0.05	0.16	0.20
Height (cm)	0.13	0.00	0.04
Weight (kg)	0.34*	0.38*	0.36*
Body fat (%)	0.37*	0.51**	0.24
CP Fat Ratio	0.24	0.24	-0.03
VO_2max ($l.min^{-1}$)	-0.06	-0.13	-0.08
VO_2max ($ml.kg^{-1}.min^{-1}$)	-0.37*	-0.39*	-0.29
Heart Rate (bpm)	0.21	0.17	-0.05
Systolic (mmHg)	0.11	0.01	-0.06
Diastolic(mmHg)	0.08	0.30	0.25
TC (mmol/l)	0.22	0.28	0.41*
LDL-C ($mmol.l^{-1}$)	0.18	0.22	0.32
HDL-C ($mmol.l^{-1}$)	-0.09	0.00	-0.02
LD/HD Ratio	0.23	0.15	0.31
Triglycerides ($mmol.l^{-1}$)	0.41*	0.37*	0.47**
Smoking (cig./day) (N=12)	0.24	0.34	0.42
Coffee (cups/day) (N=41)	-0.02	0.15	0.13
Alcohol (gl./day) (N=31)	0.07	0.16	0.15

*) $p < 0.01$, **) $p < 0.001$

Before investigating the effects of training, we determined the relationship between PAI activity and all other variables. Table 9 shows these cross-sectional correlations, that were computed separately for measurements at 0, 4 and 8 months into the study, combining the data of all four groups. These correlations therefore do not take into account the subject's training status at the time of measurement. Cross-sectional data at the initial measurement (0 months) reflect the relationship of PAI activity with the other variables in a completely sedentary population. At all times there was a clearly significant relationship between body weight and PAI activity, and virtually the same relationship evolved when BMI or the percentage body fat was used. This suggests that, even in a predominantly non-obese population, high percentage body fat may run in parallel to high PAI activity. Central over peripheral fat distribution was not consistently related to PAI activity.

There was no relation between uncorrected Vo_{2max} and PAI activity, suggesting independency of PAI activity from aerobic power. The negative correlation between weight corrected Vo_{2max} and PAI activity should be interpreted with caution, since it was entirely caused by the weight correction. The other parameters of cardiovascular fitness i.e. heart rate and blood pressure were also unrelated to PAI activity. Very clear correlations emerged between triglyceride levels and PAI activity, whereas levels of LDL-C and HDL-C were not related to PAI activity. However, triglyceride levels were also clearly

related to percentage body fat at all three measurements (Session 1: r = +0.37, S2: r = +0.42, and S3: r = +0.39 respectively, p's<0.05). This suggests that the relationships of body fat and triglycerides with PAI activity may have overlapped. Indeed, multiple regression analysis on percentage body fat, triglycerides, HDL-C, LDL-C, and blood pressure showed that only triglyceride levels significantly contributed to the prediction of PAI activity, leaving the partial correlations between percentage body fat and PAI activity only marginally significant.

Of the three possible confounding variables only smoking was related to PAI activity. Smokers as a group had higher PAI activity, but within the group of smokers PAI activity was not significantly related to the number of cigarettes smoked. All repeated measurement analyses on PAI activity were done with changes in smoking behavior (quitted/started) as a covariate. No relation was found between reported alcohol or coffee usage and PAI activity.

Table 10: Relationship of aerobic fitness to anthropometric, cardiovascular, and metabolic variables. Correlation coefficients between corrected for body weight (Vo_{2max}) and the other variables have been computed separately for measurements at 0, 4 and 8 months into the study, combining the data from all four groups. These correlations are therefore uncorrected for training status.

	Vo_{2max}		
	0 month	**4 month**	**8 month**
Age (yr)	-0.27	-0.24	-0.23
Length (cm)	0.18	0.05	-0.07
Weight (kg)	-0.25	-0.33	-0.38*
BMI (kg/l^2)	-0.42*	-0.36*	-0.38*
Body fat (%)	-0.51**	-0.45**	-0.61**
CP Fat Ratio	-0.29	-0.14	-0.08
Heart Rate (bpm)	-0.15	-0.16	-0.27
Diastolic Blood Pressure (mmHg)	-0.29	-0.23	-0.23
Systolic Blood Pressure (mmHg)	0.17	0.05	0.20
TC (mmol/l)	-0.34*	-0.14	-0.23
LDL-C (mmol/l)	-0.28	-0.18	-0.21
HDL-C (mmol/l)	0.09	0.27	0.25
LD/HD Ratio	-0.35*	-0.35*	-0.34*
Triglycerides (mmol/l)	-0.39*	-0.37*	-0.50**

*) $p < 0.01$, **) $p < 0.001$

Table 10 shows the correlation of Vo_{2max} with anthropometric, cardiovascular, and metabolic variables at all three measurements for all groups combined. From the table it is clear that subjects with the largest percentage body fat were also least fit. Central versus peripheral distribution of fat did not contribute to this relationship. Neither heart rate, blood pressure, total cholesterol, or the LDL-C and HDL-C fractions were systematically related to fitness. However, the LD/HD ratio and the triglyceride levels at all times showed a positive correlation with the Vo_{2max}. When multiple regression was used to partial out the effects of weight or percentage body fat, the relation between LD/HD ratio and Vo_{2max} disappeared, suggesting that differences in percentage body fat or weight

were causing the relationship. The correlations between Vo_{2max} and triglycerides remained intact when corrected for differences in percentage body fat, but their strength decreased (r's: -0.31, -0.36, and -0.32 respectively, p's <0.05). In summary, a more beneficial lipid profile was seen in subjects with higher levels of aerobic fitness, but part of this beneficial effect seemed to be coupled to leanness.

Training effects

Table 11 displays the changes in all variables over the first and second 4 months periods for each of the groups.

Table 11: Per group changes over time for the antropometric, cardiorespiratory, hematologic and lifestyle variables. For all variables, the first colon within each group gives the change from 0 to 4 months and the second colon gives the change from 4 to 8 months. The long-term training group trained throughout the 8 months period. The de-training group trained for 4 months and then de-trained. The postponed group remained untrained during the first 4 months and trained during the second four months. The no-training group remained untrained throughout the whole 8 months period.

	long-term		de-training		postponed		no-training	
	0-4	4-8	0-4	4-8	0-4	4-8	0-4	4-8
Weight (kg)§	-1.4 [a]	0.8	-0.5	0.6	0.9 [a]	-1.6 [a]	0.02	-0.01
Body Fat (%)§	-2.5 [a]	0.3	-1.8 [a]	1.5 [a]	1.0	-2.0 [a]	-0.3	0.1
CP Fat Ratio	-0.27	0.24	-0.10	0.28 [a]	-0.21	0.29	-0.10	0.30
VO_{2max} ($ml.kg^{-1}.min^{-1}$)§	5.3 [a]	1.8	2.9 [a]	-0.4	0.3	6.1 [a]	-1.4	1.4
Heart Rate (bpm)§	-6.8 [a]	3.4	-9.5 [a]	7.0 [a]	0.4	-4.0 [a]	-2.3	2.7
Diastolic BP (mmHg)§	-3.2 [a]	1.3	-4.6 [a]	5.0 [a]	0.1	-2.6 [a]	-0.6	1.7
Systolic BP (mmHg)	-2.3	2.4	-1.1	0.8	-1.8	-1.0	-1.1	2.3
TC ($mmol.l^{-1}$)§	-0.24 [a]	0.07	-0.47 [a]	0.42 [a]	0.02	-0.12	0.23 [a]	-0.09
LDL-C ($mmol.l^{-1}$)	-0.37 [a]	0.11	-0.42 [a]	0.39 [a]	-0.09	-0.04	-0.02	-0.04
HDL-C ($mmol.l^{-1}$)	0.13 [a]	0.01	0.00	0.01	0.07	0.11 [a]	0.01	0.09
LDL/HDL Ratio	-0.49 [a]	0.10	-0.37 [a]	0.35 [a]	-0.18 [a]	-0.17	0.02	-0.31 [a]
Triglycerides ($mmol.l^{-1}$)	-0.02	-0.13	-0.08	0.04	0.12	-0.20	0.37	-0.15
PAI activity(%)§	-24.5	-12.7	-39.8	-0.01	100.4	-74.6	39.5	-33.3

§ Significant group(4) x months(3) interaction (p<0.05)

[a] Significant change from 0 to 4 or 4 to 8 months (p<0.05)

Examination of Vo_{2max}, heart rate and diastolic blood pressure clearly suggested that cardiovascular fitness had been successfully manipulated according to group assignment (see previous chapter). In addition, there were significant Group by Months interactions for body weight ($F(6,84)=3.18, p < 0.007$) BMI ($F(6,84)=3.13, p <0.008$), and percentage body fat ($F(6,84)=7.71, p <0.0001$). Although training consistently induced weight loss, the effects were small in the de-training group, and the significant Group by Months interaction was in part due to the gain in weight that was seen in the postponed group during the first four months of the study. The training effects on percentage body fat, as measured with the skinfolds method, were more clear cut. Training reduced body fat with an average 2.2 percent in the two groups that trained during the first four months, whereas no change or a slight increase in percentage body fat was seen in the two no-training groups. During the second four month period, training reduced body fat by 2.0

percent in the postponed training group, whereas de-training reversed the previously induced decrease in percentage body fat in the de-training group. No changes were seen in the no-training control group. In spite of the decrease in percentage body fat, there was no effect of training on the central to peripheral fat ratio, expressed as the sum of brachial skinfolds versus truncal skinfolds.

There was a significant Group by Months interaction on total cholesterol levels ($F(6,84)=2.18$, $p < 0.05$) that again closely followed our training manipulations. As a consequence of de-training, total cholesterol levels completely returned to pre-training levels, suggesting that continued training is needed to maintain the beneficial training effect. Training also tended to reduce the levels of LDL-C and the triglycerides, and to increase HDL-C. However, none of the Group x Months interactions on these parameters attained statistical significance, due to the non-training related shifts in these parameters in the postponed and no-training control groups.

In the course of the study none of the groups reported significant changes in the average number of cigarettes smoked, cups of coffee consumed daily or weekly alcohol consumption.

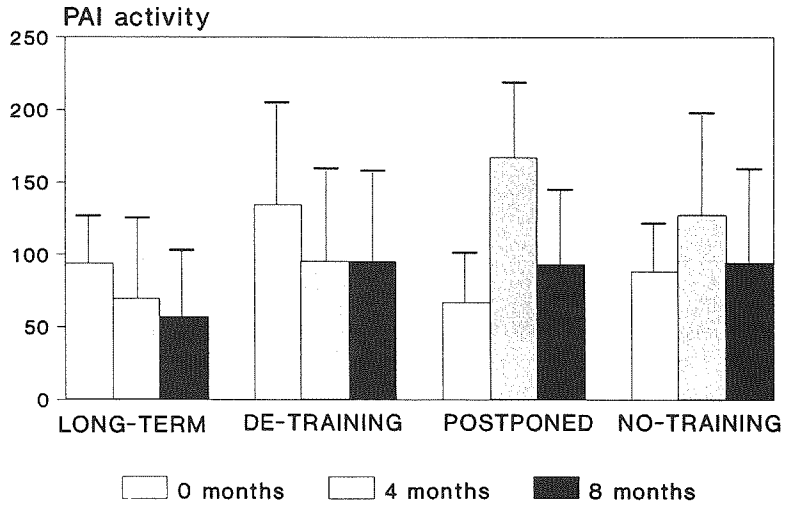

Figure 12: Group means (± 1 standard deviation) of PAI activity at 0, 4 and 8 months. PAI activity was assayed according to Verheijen et al.[592] and expressed as a percentage relative to a pooled plasma standard.

The MANCOVA on PAI activity yielded a significant Group x Months interaction ($F(6,82)=2.28$, $p < 0.05$). From figure 12 it can be seen that PAI activity always decreased in response to training. PAI-activity decreased throughout the entire training period in the long-term training group and four months of training reduced PAI activity in both de-training (0 to 4 months) and postponed training (4 to 8 months) groups. Although

these within-group effects failed to reach significance, due to the large within-group variance, this pattern of results at first sight suggests that the significant Group X Months interaction was due to our training manipulation. However, during the first 4 months of the study, both control groups showed an unexpected increase in PAI activity, contributing strongly to the Group x Months interaction over that period. Furthermore, de-training failed to increase PAI activity to pre-training levels. Therefore, in spite of the systematic reduction in PAI-activity after training, the evidence for a causal relation between training and PAI activity was incomplete.

Since training induced multiple changes in mutually dependent variables we did two additional analyses. To remove the effect of changes in body fat on changes in other variables, all analyses were repeated, using changes in percentage body fat as a covariate. No change in the pattern of results occurred, excepting the effects of training on total cholesterol. Using changes in percentage body fat as a covariate weakened the training effect on total cholesterol, although a trend was still present ($F(6,80)=2.05$, $p=0.08$). A second additional analysis assessed the simultaneous training effects on diastolic blood pressure, systolic blood pressure, body fat percentage, HDL-C, LDL-C, triglycerides, and PAI activity. This multivariate cluster reflects a set of meaningfully related parameters recently described in the literature as the "syndrome X".[468] MANOVA yielded a highly significant multivariate Group by Months interaction ($F(42,86)=2.40$, $p <0.0001$) on this cluster, and within-group effects of the training and de-training manipulations also became far more pronounced with the multivariate approach. Only in the no-training group no multivariate changes over time could be detected. The potent multivariate effects reflected the fact that, in all trained subjects, training simultaneously induced beneficial changes in one or more of these risk variables.

Interrelationships between changes in PAI activity and changes in other variables

Apart from elucidating the effects of training on PAI activity, a second aim of this study was to relate changes in PAI activity over the training period to simultaneous changes in cardiovascular fitness, body composition, triglycerides and the cholesterol fractions. In order to do this, correlations were computed between changes in PAI activity during the training phase and training-induced changes in the other variables. Only the changes in TC ($r = +0.40$, $p=0.003$), HDL-C ($r = +0.39$, $p=0.003$) and LDL-C ($r = +0.40$, $p=0.003$) during the training phase were significantly related to changes in PAI activity. Note that correlations of changes in PAI activity to changes in HDL-C, LDL-C and TC all had a positive sign in spite of the fact that LDL-C and TC decreased during training, whereas HDL-C increased. Multiple regression analyses showed that the changes in the two cholesterol fractions together could account for only 20 % of the changes in PAI activity. There was no relation to changes in any of the other variables or the total number of hours trained to the magnitude of training-induced PAI decrease.

In contrast to their meager relation to the training effects on other variables, training effects on PAI activity were clearly dependent on the initial level of PAI activity at entrance to the study ($r = -0.49$, $p <0.05$). In general, subjects with high initial PAI activity showed a strong reduction in response to the training program.

Discussion

The present study aimed to determine the effects of training on PAI activity, and to link these to changes in cardiovascular fitness, body composition and the lipid profile. The consistent reduction of PAI activity after training at first sight suggests that PAI activity may be lowered by regular exercise. That would confirm previous cross-sectional correlation of exercise status and PAI activity.[541] It is also in agreement with the findings of earlier training studies that reported similar effects of training, alone[154, 559] or in combination with smoking cessation.[219] However, the absence of a de-training effect on PAI activity in the present study seems to contradict a causal effect of training on PAI. Gris et al. did find a reversal of training effects on PAI activity during the subsequent de-training phase.[219] They also showed that after intense training, one session a week was enough to maintain low PAI activity. Perhaps de-training was not complete in our subjects, who were encouraged to keep up some form of light exercise during the first 1.5 months of de-training to prevent withdrawal problems. The failure of Vo_{2max} to revert to baseline may suggest that de-training was indeed incomplete, but reversal of cholesterol, heart rate and blood pressure training contradicts this. The fact that subjects continued smoking cessation during the de-training phase may be an alternative explanation for the de-training effects in the study of Gris et al.[219]

In the study of Estellès et al.[154] training was concluded to prevent deterioration of fibrinolysis in CHD patients. Interestingly, PAI activity did not decrease in the exercised patients, but gradually increased over time in the non-exercised control patients. The authors seem to implicitly take the increase in PAI activity as the natural cause in coronary artery disease. However, clear seasonal shifts in PAI activity have recently been reported in patients with rheumatoid arthritis[392] , whose PAI activity was much higher during the winter than during the summer. In the present study, using healthy young subjects, there was also a spontaneous increase of PAI activity in the two non-exercising control groups. Over the first 4 months of the study, that ran from February to June, PAI activity nearly tripled in the postponed training group. There is no easy explanation for this spontaneous shift in PAI activity over time. It could be argued that there may exist slow periodic changes in PAI activity, apart from the well-known circadian rhythm.[311] Furthermore, diet studies have shown that a reduction in total caloric intake has a beneficial influence on PAI activity.[264] Although dietary habits had been assessed with a three-day diary, the initial dietary habits the start of the study were lost and only incomplete information on dietary habits was obtained. Therefore, the unexpected gain in weight seen in the postponed training group during the non-training phase may well reflect an increase in caloric intake. At least in the postponed group, part of the spontaneous shift in PAI activity could be related to such a change in diet. Alternatively, the shifts in PAI activity in the control groups may simply reflect chance effects, since the interindividual variation in PAI activity was substantial. It should be noted that, in comparison, the changes in PAI activity after 4 months of training were relatively small (26%-40%) and even failed to reach significance. Clearly, much larger group sizes may be needed to detect the influence of training on PAI activity. Also the fact that blood samples were taken up to 8 days after the last training may have led to some decay of the

training effect.

Pending a satisfactory explanation for the spontaneous shift in PAI activity in the control groups, it seems unwise to interpret the significant Group by Months interaction as clear cut evidence for a training effect on PAI activity. Such an interpretation is even further complicated by the lack of de-training effects on PAI activity, and the fact that the within-subject decreases in PAI activity in the course of training were not meaningfully related to training-induced changes in cardiovascular fitness, metabolic parameters or the number of hours trained. Instead, training-induced changes in PAI activity depended strongly on initial levels of PAI activity. This is reminiscent of the findings of Stratton et al.[559] , who, after 6 months of intensive training, found no significant reduction in the PAI activity of adolescents, whereas PAI activity in a subgroup of older subjects markedly decreased. The initial levels of PAI activity were clearly higher in these older subjects. Furthermore, from their results it was clear that, in both age-groups, decreases in PAI-activity were largest in subjects with the highest initial levels, which corresponds well to our own findings. Although this may represent simple regression toward the mean, it may alternatively suggest that subjects at risk will have the most benefit from training. Future research on healthy subjects with elevated levels of PAI activity is needed to clarify this issue.

The reduction of diastolic blood pressure, body fat and total cholesterol corroborates previous research in these areas.[577, 227, 55] The fact that triglycerides, LDL-C, HDL-C, and the LD/HD ratio only tended to be improved after training confirms previous suggestions that long-term training may be needed to get the kind of clearcut differences in the lipid profile as seen in the cross-sectional comparison of high and low fit subjects.[616] Longer term exercise habits may also be needed to get a robust training effect on PAI activity. In fact, changes in lipid metabolism and body composition may be a necessary condition for changes in fibrinolytic parameters. Recently, Reaven[468] has united a set of metabolic disorders under the label of "syndrome X". Syndrome X is thought to consist of: 1) obesity with central fat distribution, hyperinsulinaemia, impaired glucose tolerance and type II diabetes 2) increased triglyceride and VLDL-C, increased LDL-C and decreased HDL-C; 3) hypertension. By now, many studies have demonstrated a close relation between high PAI activity or low fibrinolytic activity and the other symptoms of the syndrome X[394, 589, 281, 282] , suggesting it should be extended with a fourth component of 4) increased PAI activity and decreased fibrinolytic potential. The clear correlational relations between triglycerides, percentage body fat and PAI activity in the present study are in support of this, although the relationship between cholesterol and PAI activity was only meager.

Due to the synergistic effect of the syndrome X variables on vascular pathology, a simultaneous reduction in all these variables may be more effective in reducing the risk for cardiovascular disease, than the reduction of a single risk factor. When percentage body fat, lipids, blood pressure and PAI activity were jointly analyzed in the present study, it could be shown that training consistently reduced the threat posed by the cluster these variables, even though the effects on a single variable were unimpressive. The joint effects of training on the syndrome X variables closely resemble the effects of metformin, an insulin targeting drug, or of third generation β-blockers. All these drugs

reduce blood pressure and improve the lipid profile while at the same time increasing fibrinolytic potential.[281, 243] If these effects reflect a common pathway, then increased insulin-sensitivity seems to be the most critical factor.[468] Therefore, future research on the beneficial effects of exercise training should concentrate on its joint effects on insulin metabolism and fibrinolytic parameters.

In summary, cross-sectional analyses showed PAI activity to be associated with high levels of triglycerides and body fat. Vo_{2max} was associated with low PAI activity, low body fat percentage, and low levels of TC, triglycerides and the LD/HD ratio. PAI activity always decreased in response to training, but spontaneous seasonal shifts were seen in the postponed and no-training control groups, and de-training failed to influence PAI activity. We conclude that exercise training may help to lower PAI activity, particularly in subjects with high PAI levels, but that more control over seasonal shifts is needed to establish definite causality. The occurrence of simultaneous changes in body fat, blood pressure, lipid profile, and PAI activity underscores the potential of regular exercise to protect against cardiovascular disease.

8. General discussion

The main goal of this thesis was to show that regular exercise counters the detrimental effects of stress on cardiovascular health. In order to protect against stress-related disease, exercise was hypothesized to have all of the following effects: 1) improve psychological coping with stress, 2) reduce physiological reactivity to stress, and 3) counteract the effects of stress on the cardiovascular risk factors (heart rate, blood pressure, cholesterol, PAI activity). These various psychological and physiological effects of exercise have often been examined separately, and published in different areas of the scientific literature. Effects of exercise on cardiovascular risk factors traditionally belong to the area of (applied) physiology (e.g. J. Appl. Physiol., Circulation) and sports medicine (e.g. Med. Sci. Sports Exerc.). Psychological effects of exercise are predominantly found in journals related to health psychology and sports psychology (e.g. Health Psychol., Int. J. of Sports Psychol.), whereas 80 % of the studies on the psychophysiological effects of exercise have been published in three journals only (Psychophysiology, Psychosomatic Medicine, J. of Psychosomatic Research). Nonetheless, numerous cross-links between the various effects of exercise can easily be conceived of. For instance, improved psychological functioning may be the basis of reduced blood pressure reactivity to stress, and the lowered reactivity may play an important role in the lowering of blood pressure. Vice versa, low reactivity (no palpitations, sweating, etc.) may increase perceived efficacy to cope with a stressor and, in the long run, improve psychological make-up. In my own research, I have aimed at an integration of psychological and physiological training effects by measuring them concurrently in the same population. This raised a serious methodological problem since it amounted to a large number of variables, even exceeding the total number of subjects. In spite of the huge amount of correlations, surprisingly little correspondence was found between changes in psychological make-up, stress-reactivity and risk factors. Empiricism itself seemed set to oppose an interdisciplinary approach. As a consequence, I too have fallen back on enumeration of the various exercise effects, rather than integration. This was already reflected in the outline of the whole thesis and returns in full in this general discussion. First, I will discuss cause and effect with regard to the different psychological make-up of exercisers and non-exercisers. Next, I will comment on the studies on fitness training and stress-reactivity. Finally, after a re-evaluation of the reactivity hypothesis, I will discuss the implications of our results for the usefulness of exercise programs to counter cardiovascular disease.

8.1. Psychological make-up of exercisers

Traditionally, research on the relationship between exercise and psychology has focused on the prediction of athletic success from personality characteristics. Although there appear to be systematic differences in the personality of sporters vs non-sporters[407] , these differences are generally smaller than those linked to individual preferences for different type of sports. Sprinters for instance are said to be more neurotic than endurance athletes, and the marathon will attract a different personality type than

car-racing or chess. Several authors have criticized the structural static approach of trait psychology, and they claim that personality cannot predict sports participation or sports performance very well.[378] Nonetheless, if we concentrate on endurance type sports, some meaningful distinction in the personality between athletes and non-athletes can be made. Generally, endurance athletes are found to be less neurotic and more extraverted than non-athletes[179, 489, 156, 348, 349, 186] and, above all, have adequate self-discipline to adhere to an exercise regime.[312] With regard to mood state, athletes systematically show the "ice-berg" profile.[406, 408] They experience lower tension, depression, fatigue, and confusion than the average population, and have more vigor. The ice-berg profile has indeed been found to be most pronounced in the successful athletes, reviving the idea that a good psychological state is essential to athletic performance.[408]

Most of the studies on athletic personality have implicitly assumed selection as the main reason for differences between (successful) athletes and non-athletes. Personality is seen as a pre-requisite for, rather than a consequence of competitive exercise behavior. Recently, attention has shifted to an alternative possibility: that regular exercise itself causes beneficial changes in psychological make-up. These effects are probably not characteristic of competitive (top)sport, but they may play an important role in recreational exercise. Psychological benefits attributed to sports and exercise as a recreational past time have been manifold. Exercise has been seen as a way to influence mood (anxiety, depression, anger), personality (emotional stability, extraversion, independence, rigidity) cognition (intellect, memory, perception, creativity), self-concept (body image, self-confidence, self-efficacy, self-esteem), coping style (type A, anger-handling), work performance (absenteeism, productivity, corporate image) and stress-related symptomatology (headache, dysmenorrhea, alcohol abuse).[179, 262, 253, 582, 160] Particularly the idea that exercise reduces the subjective experience of stress and subsequent physiological stress-reactivity, has attracted many believers. How can we explain this commonly held belief in the stress-alleviating effect of exercise (that so clearly contrasts with experimental evidence on stress-reactivity)? One possible answer lies in the improved mood that is consistently found directly after an acute bout of exercise.

Acute psychological effects of exercise

Directly after exercise, confusion, tension, anxiety and anger are all decreased, accompanied by increased feelings of energy and vigor.[19, 481, 465, 53, 551, 482, 315] This acute "feeling better" effect of exercise is paralleled by various physiological effects. Although heart rate generally remains elevated above the base level[137, 176, 172] , post-exercise blood pressure is seen to decrease below base level for several hours[465, 445, 176] , and this effect is particularly strong in hypertensives.[175] Neuromuscular activity (EMG) and peripheral pulse volume are decreased[172, 596] , and brain alpha activity, an indicator of a relaxed but alert mental state, is increased.[53] Among the hypothetic mechanisms for the neurophysiological effects of exercise, those related to the endogenous opioids have been most often cited.[466] Of special interest is the β-endorphin system which contributes to the regulation of blood pressure, pain perception, and the control of body temperature. During and directly after exhaustive

exercise the plasma levels of β-endorphin are increased (e.g.[573, 134]) and this is accompanied by an elevation of the pain threshold and improvement of mood. β-endorphins are generally held responsible for the euphoric (after)effects of running, that have been ominously termed "runner's high".[488] The possibility of a benign endorphin-mediated addiction to running has received support from studies on regular exercisers who were forced to quit exercising through injuries, or as part of an experiment.[410, 528] Cessation of exercise led to severe mood deterioration and increased reports of physical discomfort. However, the mood loss seen in these studies may reflect the loss of fulfillment of the athlete's reasons for participating in sports and exercises, and does not necessarily suggest an opiate withdrawal syndrome. Indeed, the opiate antagonist naloxone does not prevent the exercise-induced elevation in the pain-threshold or the mood improvement, suggesting that these are largely independent from endorphin action.[164, 375, 134] More importantly, peripheral endorphin level consistently increases during strenuous exercise only, but not during mild to moderate exercise. It seems to depend on the perception of exercise intensity, i.e. expectation of future pain and exhaustion. This is not surprising, since β-endorphin is a typical stress-hormone (often co-released with ACTH), and elevations in its level are normally associated with negative rather than positive mood, even during exercise.[315]

Some caution is in order with the conclusion that endorphins are not responsible for any of the acute effects of exercise. Most of the studies using pre-treatment with naloxone have used inadequate low doses to block the action of all endogenous opioids. In addition, changes in peripheral endorphin levels do not necessarily mirror changes in endorphin concentration in the brain and the spinal cord. Changes in central endorphin do seem to play a role in the post-exercise fall in blood pressure.[573] In animal models, prolonged muscle stimulation was seen to give rise to a post-stimulatory drop in sympathetic nerve activity and blood pressure, that was particularly strong in spontaneous hypertensive rats.[617, 618, 514] These effects could be entirely abolished by naloxone. It is possible that there is a gradual increase in central opioid action during prolonged submaximal exercise. Opioid action is known to cause a reduction in central sympathetic outflow, and increased parasympathetic activity.[51] As long as exercise continues, the tendency toward reduced sympathetic activity is probably countered by central feed-forward and muscle-feedback. Upon cessation of exercise, the sympathoinhibitory effect becomes manifest, and this may cause the reduction in blood pressure. In fact, direct evidence of reduced sympathetic vasoconstriction in skeletal muscle after exercise has been found in borderline hypertensives.[175] Whether changes in central opioid action on sympathetic pathways also influence mood remains speculative.

Since monoaminergic systems in the brain are involved in the pathogenesis of depression and anxiety, an alternative explanation for exercise-induced mood effects may reside in its effect on central monoamines. Exercise increases noradrenaline and dopamine metabolism in the brain, possibly by activating the rate-limiting enzyme in DA/NA synthesis, tyrosine hydroxylase, and it may also increase brain serotonin content.[83] It shares these effects with antidepressiva like tricyclics and MAO inhibitors, that, like exercise, also shorten REM sleep and promote delta sleep.[466] The effects of exercise on monoamine synthesis may well interact with the proposed effects of the central

opioids on blood pressure. Serotonin antagonists, for instance, were seen to block the hypotensive effects of muscle stimulation.[618] Whether the action of monoamines and endorphins also combine in the mood effects of exercise is as yet unclear. In general, it seems unlikely that the short-term mood effects of exercise stem from its pure physiological effects alone, be they increases in monoamines and endorphins or otherwise. As Ransford pointed out, there is a time lag of several days between the administration of antidepressant medication and changes in self-reported depression, even though antidepressants affect adrenergic synaptic transmission almost instantaneously.[466] Cognitive factors appear to play an important role in the effect of antidepressants, and there is no reason to suspect it to be otherwise in the case of the neuropsychological effect of exercise. In a naturalistic setting, playfullness and social interaction will enhance the joy in sports and exercise. Even in the laboratory, simply reading a magazine has been shown to reduce anxiety as much as exercising[19] , suggesting that exercise-induced relaxation may be partly a consequence of diversion of attention or "time-out". Important cognitive modulation of the exercise effects was further confirmed by the fact that reduced anxiety after exercise was predominnatly seen in regular exercisers, but less so in inexperienced runners.[53]

Whatever its physiological and psychological causes, the tight contingency between exercise and the mood improvement afterwards would form a solid basis for the popular belief that exercise relieves stress. It confirms the notion that exercise may be an excellent short-term coping strategy that helps us unwind more rapidly from daily pressures experienced in the school, job or home environment. Some have suggested that the beneficial psychophysiological effects of exercise are also limited to the hours directly after the exercise.[233] Although several studies did not find a reduction in the physiological reactivity to stressors presented directly after an acute bout of exercise[485, 520, 137, 481] , more recent studies did report such effects.[484, 435] In a study by Roy and Steptoe, 20 minutes of exercise reduced the heart rate and blood pressure responses to mental arithmetic.[484] The reduction in responsiveness was stronger if the exercise was of higher intensity (defined as a percentage of maximal capacity). The accumulation of such episodes of blunted responsiveness may reduce the health risks of stress, even if reductions in reactivity are confined to stressors in the post-exercise periods. Surprisingly, the acute effects on stress-reactivity were independent of perceived stressfulness of the task. In fact, the subjective experience of stress was found to be unchanged after a bout of exercise in this and all other studies.[520, 137] Apparently, the reduction in cardiovascular responsiveness reflected a physiological after-effect of exercise, that is possibly related to the overal reduction in blood pressure level. These effects may be caused by opioid and monoamine mechanisms, as discussed above, by a down-regulation of the cardiac β-adrenergic receptors[196] , or by the general increase in vasodilating metabolites.

Psychological effects of training.

From a psychosomatic viewpoint, the acute effects of exercise are less interesting than the possibility that regular exercise has lasting effects on psychological functioning,

affecting the physiological response to stress in general, rather than specifically after exercise. This does not automatically follow from the post-exercise increase in mood or reduction in blood pressure, since these effects are known to wear off within a short time (2-5 hours). Instead, exercise should yield profound changes in general well-being and the psychological ability to cope with stress, which are not limited to the acute exercise situation. If fitness programs were shown to improve coping with real-life stressors, then the lack of effects on the amplitude of physiological stress-responses would be less cumbersome. Reduced frequency and duration of the stress-response would amply compensate the fact that the intensity of the stress responses was unchanged.

Several psychosocial mechanisms have been proposed that could explain such lasting effects of exercise. According to Sonstroem and Morgan[536] , regular exercise will start by enhancing the belief that one is capable of performing certain physical activities. This increase in physical self-efficacy, together with true improvements in endurance capacity, flexibility, and body composition, will improve physical self-confidence and physical self-acceptance, and my finally generalize to improvements in global self-esteem. In addition, the process of setting and achieving goals will lead to a sense of competence and mastery.[218] This may generalize to situations outside exercise and improve global self-efficacy and perceived coping skills.[350, 351] These effects are further enhanced by an increase in social self-esteem, when sports behavior enhances self-identity by the feeling of belonging to a supportive group with shared values, interests, and activities. Most of this theorizing justly choose to focus on self-esteem, since self-esteem (or self-concept) has consistently been shown to improve through exercise.[179, 262, 535] Furthermore, by focusing on self-esteem it also allows for an explanation of the single most acclaimed effect of exercise: reduced depression. Most theories of depression link it to negative self-esteem. For instance, in the learned helplessness theory, depression is thought to arise from the repeated experience of failure that decreases the sense of personal worth, and induces the belief that one has no talents and little control over one's own life. By regularly providing feelings of succes, mastery and efficacy, training may counter the development of helplessnesss, and alleviate feelings of depression.

In spite of the elegant reasoning, these theories can only derive validity from empirical testing of exercise effects in large groups of subjects. Although there is an abundance of both anecdotes and research papers supporting the notion that exercise yields psychological benefits, most authors in the field will agree that much of these reports suffer from severe methodological flaws (e.g. Hughes[262]). The more recent studies have conscientiously tried to correct these. Often the effectiveness of the exercise regime is now often compared to a placebo treatment, which may consist of training in stress-management, meditation, muscle-relaxation, or of a non-aerobic exercise program that aims to increase strength or flexibility, rather than aerobic fitness. These alternative treatments are meant to prevent interference of subjective expectations, distraction, social attention/interaction, and trainer enthusiasm with the outcome of the exercise training per se. The subjects are not allowed to choose between these treatments, but are randomly assigned to either aerobic training or control treatment. The rationale behind this random assignment is that, if subjects are allowed to choose their own treatment, only subjects

who are enthusiastic about starting exercise training will enter the training group, whereas those who have no interest in exercising will tend to choose the alternative treatments. This may cause self-selection of subjects with a specific psychological make-up or a relatively high aerobic endowment into the training group. Such self-selection may blur the effectiveness of the training program to bring about physiological changes, since progress will be lower in high fit subjects. At the same time self-selection may exaggerate psychological effects, since expectancy of positive exercise effects will be largest in those who choose to exercise.

Both the usage of a placebo treatment and the random assignment of treatment groups have been gratuitiously adopted from clinical research on new therapies and drugs on psychiatric or medical patients. In spite of our methodological sophistication we must not be tempted to forget that, unlike patients, subjects in this kind of research are volunteers. Generalizability is necessarily limited to the subset of volunteers willing and able to take up exercise training. Many people consider exercise to be an unpleasant activity, especially at the outset of training regimes, and even more people fear the substantial risk for harm and injury. Subjects recruited in exercise research probably do not belong to this class. They are likely to have had previous (positive) experience with exercise and to be highly motivated to take up exercise. For instance, the average attrition rate in the studies referenced throughout this thesis was 77 %. This is far better than the 30-40 % attrition rate quoted for subjects who participate involuntarily in exercise programs (cardiac patients, weigth reduction).[121] There is no way we can tell how the results from the exercise studies cited generalize to the population at large. It is likely however, that participants in these studies are biased toward expecting positive exercise outcomes.

The "correction" for positive expectations, attention, social interaction, distraction and trainer enthusiasm by the use of placebo treatment seems methodologically highly elegant. But should it be done and can it be done? Such correction leaves the physiological effects of exercise, in particular the increase in fitness, as the main determinant of psychological changes. However, an increase in aerobic fitness may not be relevant at all (see chapter 6). In our zeal to remove the effects of social interaction and distraction, we may also remove the most plausible mechanisms by which exercise benefits us psychologically. Trying to correct the effects of positive expectation and trainer attention/enthusiasm is even more hazardous. There are large differences in physical capacity and in the ability to improve it ("trainability"). It seems unavoidable that physical capacity, will interact with the perceived pleasantness of exercising. How can body-image and physical self-confidence improve, if others, presumably as untrained as oneself, suddenly start to perform much better? Some subjects may be insensitive to being the all-time loser of the class, and happy just to achieve the goals they have set for themselves. There will be little chance of psychological improvement in such persons. They have already reached a superb psychological balance according to virtually any definition of "adequate personality"! The alternative for the less talented subjects is to drop out of the program. Dropping out may well leave the person with feelings of failure and lowered self-esteem, and the trainer (particularly in patient research, where trainer is therapist alike) is under moral obligation to give extra encouragement and positive

feedback to such subjects. In addition, differences in exercise capacity should be further smoothed by tightly matching the training program to the individual. Undoubtedly this will raise the adherence levels and improve the chances of finding psychological exercise effects. To what extent however, is such an exercise program still comparable to the alternative treatments?

Although the methodological issues sketched above remain unresolved, the recent research on exercise and psychology has yielded a fairly consistent pattern of results. As reviewed in chapter 6, it suggests that pre-training psychological disturbances are a prerequisite to benefit from exercise. These disturbances may be largely dispositional (neuroticism, low self-concept), but a high level of work-stress and daily hassles may also increase the chance of beneficial exercise effects. Dependency of psychological training effects on subject selection would easily be reconciled with psychosocial explanations of the exercise effects. The increased self-efficacy in combination with the experience of belonging to a cohesive supportive group, and the positive reinforcement of peers and family, may be particularly useful in high anxious or depressed persons. Indeed, running therapy has been proven an effective way to counter depression in various studies using depression patients and students scoring high on depression inventories.[45] Furthermore, "time-out" distraction effects may be most pronounced in subjects experiencing high levels of daily stress, and these subjects are probably also the most sensitive to the acute stress-alleviating effect of exercising.

Without denying the potential of exercise as a therapy in isolated subjects, there is good reason to challenge the idea that exercise training will induce profound changes in psychological functioning in large groups of subjects. The ineffectiveness of exercise programs to change the psychological make-up of the population at large was perhaps best demonstrated in the US National Exercise and Heart Disease project.[556] In this study, no improvements in anxiety and depression were noted after training by 651 exercisers or their spouses. These results are well in accordance with the findings of our own training studies, where no effects on anxiety (chapter 5) or a broader set of psychological variables (chapter 6) were found in a previously sedentary population with a normal psychological profile. Trait-like personality characteristics ("temperament"), like extraversion, neuroticism and hostility, are even less likely to be influenced.[179, 262] Furthermore, there is little evidence for improved cognitive functioning through chronic exercise. Speed of response may improve after exercise, but tests of reasoning and memory are inconclusive.[85] The idea that regular exercise may specifically prevent loss of cognitive functions in the elderly was contradicted by Blumenthal et al.[39] They administered a comprehensive psychological test battery including measures of psychomotor, memory and perceptual abilities before and after an exercise program. Although a host of physiological benefits were found (Vo_{2max}, cholesterol, blood pressure), exercise did not influence neuropsychological functioning.

It is possible that the beneficial effects of fitness programs transcend changes in individual psychological make-up, and involve much broader psychosocial effects, for instance when a fitness program is implemented at the work-site. Several mechanisms have been proposed by which exercise may influence work-stress and job dissatisfaction.[97] Subjective appraisal of stress in the work situation depends strongly on the

individual's perception of work capacity and job demands. By increasing physical work capacity it may reduce the subjectively appraised discrepancy between work capability and job demands. Furthermore, corporate fitness programs may function to improve social traffic and communication between workers among themselves, and between the work-floor and management. They may also improve the corporate image and help to increase job-involvement and job-satisfaction. Note that these exercise effects do not necessarily assume a true change in psychological make-up nor even cardiorespiratory endurance of the subject. They rely completely on changes in subjective perception of the work situation (or even on the expectancy of beneficial effects of exercise).

Unfortunately, large scale field-studies determining the effects of corporate fitness programs on the impact of work-stress are scarce, with adequate control groups often lacking. There is not much doubt about the fact that those who volunteer for corporate fitness programs report less stress[433] , are more productive[27] and are less often sick.[96, 446, 54, 337] However, these differences appear to reflect selection rather than an effect of fitness training itself.[54, 27, 433, 141] The few studies that used a longitudinal design did not find much effects on subjective well-being[433] or productivity.[27, 475] The only consistent effects of corporate fitness programs are found in the more objective health indices, like heart rate[68, 301] , blood pressure, and[68] body composition.[301, 54] Particularly in the field of corporate fitness training, some scepticism is warranted on the use of exercise as a psychological panacea. Little is known about the cost-effectiveness of exercise training as compared to other intervention programs like management skills training, or relaxation and mediation based programs. These programs may be more effective than exercise in reducing stress at work[68] but easier to implement, with a far smaller risk for sick leave through sports-related injury. Furthermore, blind faith in the stress-reducing properties of fitness training could prevent the organization to detect and alleviate the root causes of work-stress. In the worst case, fitness training could be even used to relieve the management of its responsibility to do so.

Determinants of exercise behavior

Taken together, the data in this field suggest that psychological differences between 1) athletes and non-athletes, 2) recreational sporters and sedentaries, and 3) corporate fitness programs participants and non-participants, largely reflect self-selection. This basis of this self-selection may be manifold. Since lack of leisure time is the most quoted reason for not exercising or for dropping out of supervised exercise programs[549, 121] , high work pressure may be an important obstacle for sports participation. However, regular exercisers are as likely as sedentaries to view time as an activity barrier, and working women are even more likely to exercise than are non-working women.[549, 121] Access to facilities and organized activities are also perceived as important facilitators of community sports and exercise participation, but true proximity to exercise facilities does not seem to predict who drops out of an exercise program, and who doesn't.[201] Therefore, lack of time and inconvenient facilities may in part reflect rationalizations of a lack of motivation or discipline to be active. Lack of self-discipline is in fact the second most important reason given for not exercising. A simple questionnaire of "self-motivation"

has been consistently related to exercise participation by Dishman and coworkers.[119] They define self-motivation as a general disposition to persevere at a task, and consider it to reflect willpower and self-regulatory skills, such as effective goal setting, self-monitoring of progress and self-reinforcement. Endurance athletes have consistently scored high on self-motivation, and self-motivation has discriminated between adherents and dropouts across a wide variety of settings, including athletic conditioning, preventive medicine, cardiac rehabilitation, commercial spas and corporate fitness programs.[121] In addition, the self-motivated person may be most likely to adopt problem-focused coping, and to persevere until a stressful situation is brought under control, rather than to revert to less desirable coping strategies like problem avoidance and depressive responding. Thus, self-motivation and self-regulatory skills may link exercise behavior directly to stress-resistance.

Apart from self-motivation, there are various socio-economic, dispositional and attitudinal factors that may explain why exercise behavior and mental health covary (reviewed in Dishman[121] and Jex[277]). Instead of re-examining the psychological effects of training, it may be wiser to study the (psychological) determinants of exercise behavior. Understanding why people do *not* exercise, or drop out of exercise programs, might permit the development of training programs that encourage persistent changes in exercise behavior. For the recruitment of large segments of the population into exercise programs, emphasis on improved physical health and weight loss may be more effective, or at least more honest, than the promise of improved well-being. The important role of self-selection in exercise behavior does of course not exclude the possibility that, within the group of regular exercisers, exercising does lead to an improvement in mental health. Through exercise, regular exercisers may get to be even more self-confident, self-motivated and vigorous, and less prone to depression and anxiety. For some, exercise may even become an important coping mechanism that is truly important to their well-being, up to a point where stopping exercise could lead to (severe) depression. Furthermore, within the group of exercisers, strict adherence to a regular exercise regime will serve to strengthen the attitude that one's health and well-being are dependent on exercising. In fact, most of the popular ideas on the psychological benefits of exercise may stem from exercisers themselves.

8.2. Fitness training and stress-reactivity

Most of the literature cited above justly regarded an exercise-induced improvement in self-reported well-being as an important goal in itself. However, such effects would gain momentum if they were shown to reduce the physiological response to stress, because physiological stress-reactivity is widely held to be the crucial link between exercise and (cardiovascular) disease. Since stress-reactivity is dependent on the subjective appraisal of the stressor, that in turn depends on psychological make-up, it is not unrealistic to expect a training-induced change in psychological characteristics to be reflected in reduced reactivity. However, even if no psychological effects of exercise are found and the appraisal of stressors is unchanged, there is still good reason to expect a difference in the stress-response of the well-trained and the untrained. The various training-

induced adaptations to in the organization of the autonomic nervous system and its target organs, e.g. dominance of the parasympathetic over the sympathetic nervous system, greater sensitivity for hormonal cues (β-2-receptors, insulin-sensitivity), and better vascularization of muscle tissue may all critically influence physiological reactivity. By its physiological effects fitness training may still reduce stress-reactivity, even if little psychological effects of fitness (training) on stress-reactivity are found.

The main approach to study the effect of exercise in the literature has been the comparison of high fit exercisers to low fit sedentary subjects (see chapter 4). This cross-sectional comparison was a sensible exploratory step, and suggested that exercisers may indeed have lower reactivity. Unfortunately, neither the aerobic fitness level nor the psychological profile of exercisers is necessarily a consequence of their exercise habits. Psychological differences between exercisers and non-exercisers may partly reflect self-selection, and differences in fitness may largely depend on differences in genetic make-up. In our own studies, we assessed the cross-sectional association of Vo_{2max} with reactivity in all-sedentary populations. We hoped that this would allow us to separate the effects of aerobic fitness from those of exercise behavior. However, given the conflicting results of our own studies, no clear pattern can be distilled from these studies. Furthermore, the exact background of the pre-existing differences in aerobic fitness in these sedentary subjects is unknown. Most likely, they reflect genetic variance, but past physical activity habits may also have contributed. Complete separation of genetic and environmental influence on fitness can probably only be attained in longitudinal twin studies. Fortunately, the influence of aerobic fitness per se was mainly interesting from a scientific viewpoint. From a public health perspective, the main question is whether exercise programs are successful in countering the aversive effects of stress. To answer this question, training studies were needed using exercise programs with realistic frequency, intensity and duration characteristics that could be implemented on large groups of (currently inactive) people, for instance within a corporate fitness program setting.

Table 12 gives an overview of the results of 15 studies dealing with the effects of training on stress-reactivity. Most of these studies were done over the past five years, i.e. in the same time period as the studies detailed in chapter 5 and 6. Several other studies known to me were left out because (1) they used physical rather than psychological stressors[562] , (2) no estimation of relevant parameters could be made[390, 539] , (3) group sizes were lower than 5 subjects[224] , or (4) experimental design was thought inadequate.[90, 524] With regard to the latter, in particular the lack of a control group is problematical. At first sight, significant differences in stress-reactivity before and after training would suffice to "prove" a causal effect of training on stress-reactivity. However, with repeated application of the laboratory tasks, there is often a spontaneous reduction in physiological reactivity, since most stressors become less potent once they have lost there novelty.

Table 12: Summary of studies on the effects of fitness training on physiological stress-reactivity.

Study	Population				Aerobic Training			Design				Outcome	
	Subjects	Number & Sexe	Age (avg/range)	Initial VO2max (ml/kg)	Duration (weeks)	Frequency (day/wk * min.)	Effect (% fitness increase)	Training State	Grouping	Stressors	Physiological Variables	Reactivity	Recovery
Keller & Seraganian 1984	YMCA Members	30 F, 30 M	23.2 (17-40)	n.g.	10	4 * 30	Step test ↑	Mixed	20 Acrobic 20 Meditation 20 Music class(^R)	Track, Stroop	EDR	n.m.	EDR ↓
Sinyor et al. 1986	Local Residents (Quebec)	38 M	23.4 (20-30)	39.6	10	3 * 60	14.6	Untrained	15 Acrobic 15 Anaerobic 8 Waiting-list (^R)	MA QUIZ Stroop	HR	no effects	no effects
Dienstbier et al. 1987	Students	39 F	n.g.	n.g.	12	3 * n.g.	n.g.	Untrained	16 Acrobic 23 No training (^S)	Stroop, MA	NA, A in urine	NA↑,A↑	n.m.
Holmes & McGilley 1987	Students	67 F	n.g. (17-20)	n.g.	13	2 * 50	Cooper test ↑ (+7.5)	Trained/ Untrained extremes	37 Acrobic 30 No training (^S)	WAIS' IQ test	HR	low fit: HR↓	n.m.
Roskies et al. 1986	Type-A managers	107 M	37.0 (21-57)	40.3	10	3 * 40	16.4	Mixed high fit ss rejected	33 Acrobic 37 Stress manag. 37 Anaerobic (^R)	MA, MS, Quiz, Stroop	SBP, DBP, HR	no effects	no effects
Blumenthal et al. 1988	Type-A's	31 M	44.4 (31-59)	39.8	12	3 * 50	13.3	n.g.	16 Acrobic 15 Anaerobic (^R)	MA	SBP, DBP, HR	no effects	SBP↓ DBP↓ HR↓
Helin & Hänninen 1988	Students	18 F, 16 M	20.1 (n.g.)	52.0	8	4 * 35	11.5	Trained	11 Acrobic 12 Relaxation, 11 No training (^R)	Public speech	SBP,DBP, HR EMG, SCL	SBP↑, DBP↑	n.m.
Sherwood et al. 1989	Type-A's	27 M	41.4 (33-56)	33.8	12	3 * 50	13.3	n.g.	14 Acrobic 13 Anaerobic (^R)	MS	SBP, DBP, HR, CO, PEP, TPR	SV↓, TPR↑ normotens.:PEP↓ border:DBP↓	border:DBP↓
Blumenthal et al. 1990	Type-A's	35 M	42.3 (30-52)	33.6	12	3 * 50	15.5	n.g.	20 Acrobic, 15 Anacrobic (^R)	MA	SBP, DBP, HR A, NA in plasma	no effects	no effects
Steptoe et al. 1990	Local Residents (London)	55 F, 20 M	38.7 (18-60)	29.3	10	3 * 50	21.8	Untrained	18 High/19 Low 18 Anacrobic, 20 Waiting-list(^R)	RAVEN's IQ test	SBP,DBP,HR, RR, Vt, SCL	no effects	no effects
de Geus et al. 1990	Students	22 M	23.7 (18-28)	46.6	7	4 * 90	14.7	Untrained	14 Acrobic 8 Untrained	MS, TA, CP	SBP, DBP, HR, CO, PEP, TPR, RSA, RR	no effects	no effects
Claytor et al. 1991	Students	35 M	21.0 (n.g.)	48.9	10	4 * 30	16.6	Untrained	20 Acrobic, 15 Control (^S)	n.g.	CO, SV, HR, MAP, A, NA in plasma	CO ↓	n.m.
Blumenthal et al. 1991	Non-obese hypertensives	57 M 35 F	45.2 (29-59)	31.8	16	3 * 50	15.6	Untrained	39 Acrobic 31 Anaerobic 22 Waiting-list (^R)	MA,VG,CF, Public Speech	DBP, SBP	no effects	no effects
Albright et al. 1992	Lockheed employees	43 M 39 F	47.4 (40-60)	m: 32.5 f: 25.5	24	5*50	12.5 16.0	Untrained	42 Acrobic, 41 No training (^R)	MA	DBP, SBP, HR	no effects	no effects
de Geus et al. 1992 (chapter 6)	University personnel	55 M	32.7 (24-40)	45.7	16	2*50	12.0	Untrained	11 Long-term, 17 De-training, 18 Postponed, 9 Control (^R)	MS, TA, CP	DBP, SBP, HR, TPR, CO, PEP, NA, A in urine	long-term:TPR↓	no effects

Abbreviations: M=Male,F=Female, n.g.=no data given, n.m= not measured, (^R) random assignment to control and training groups, (^S) subjects self-selected to be in the training group, Track= visual tracking task, Stroop=Stroop word color conflict task, MA= Mental Arithmetic, WAIS=Wechsler Adult Intelligence Scale, MS=Memory Search, RAVEN=RAVEN's Progresive matrices (spatio-visual ability), TA=Tone Avoidance reaction time task, VG= Video Game, CP= Cold Pressor, CF= Cold Face stress, EDR=Electrodermal Activity Ratio, HR=Heart Rate, SBP=Systolic Blood Pressure, MAP=Mean Arterial Blood Pressure, DBP=Diastolic Blood Pressure, NA=Noradrenaline, A=Adrenaline, EMG=Electromyogram, SCL=Skin Conductance Level, CO=Cardiac Output, PEP=Pre Ejection Period (beta-adrenergic cardiac drive), TPR=Total peripheral vascular resistance, RR=Respiration Rate, Vt=Tidal Volume, RSA=Respiratory Sinus Arrhythmia (vagal cardiac drive).

Furthermore, spontaneous reductions in reactivity due to seasonal fluctuations, abrupt changes in the person's social environment, or simple statistical "regression towards the mean" cannot be ruled out. Therefore, the changes in reactivity after training had to be compared to the spontaneous changes in reactivity in a control group that underwent identical testing, but did not receive training. Often the control group was subjected to some kind of placebo treatment (stress-management, meditation, muscle-relaxation non-aerobic exercise), and ideally the subjects were randomly assigned to the various treatments. Clearly, it is not easy to find subjects that are willing to participate in an experiment where they will be assigned to "any treatment, but not of your own choice". Therefore an alternative approach was often used, where all subjects were allowed to participate in exercise training, but at different times. For instance half of the subjects was allowed to start immediately, whereas the other half is temporarily put on a waiting list. During their period in the "waiting room" they already partook in laboratory testing so that they could be used as a control group.

A total of 523 males and 283 females were used in the training studies summarized in table 12. About 45 % of these partook in exercise training (247 M, 114 F). The average age varied from 20 to 44 with a range of 17 to 60. Subjects in these studies were always required to be healthy and able to withstand strenuous exercise training (Clearly, this will limit generalizability of the conclusions of this review to healthy subjects in the adolescent to middle-aged range). Several studies deliberately selected subjects that were "untrained", i.e. not involved in regular strenuous activities at a frequency (3 times a week) or duration (20 min or up) required to maintain elevated levels of aerobic fitness. The effects of training programs are expected to be most pronounced in such a sedentary population. Sedentary status was often checked by using physical activity questionnaires where subjects self-report their exercise behavior over the past year.[255, 554] Several studies did not mention specific selection of sedentary subjects, but initial levels of aerobic fitness clearly suggest that most subjects were low to average fit. The aerobic training programs consisted of 2 to 4 sessions weekly over a period of 7 to 12 weeks. The training sessions were often plenary and supervised by a qualified trainer, who regularly recorded pulse rates in order to keep intensity of the exercise at a minimum of 65% to 85% of maximal capacity. Training was made up of a warming-up and stretching period followed by the actual aerobic exercise (mostly jogging or bicycle ergometry), the average duration of which was about 35 minutes. A cooling-down ended the sessions. The effectiveness of the training-programs was measured by using (estimates of) the peak oxygen consumption during a supramaximal exercise test, expressed as milliliter oxygen consumed per kg body weight (Vo_{2max}). The Vo_{2max} is generally held to be the best indicator of aerobic fitness, and is highly correlated to other indicators of endurance capacity (Cooper test, treadmill time , step test). The average improvement in Vo_{2max}, were measured, amounted to 14.8 %.

In spite of the significant increase in aerobic fitness, the effects of training on stress-reactivity or on recovery from stress were minimal (The arrowheads in table 12 reflect a significant difference in the influence of training and the alternative treatment on reactivity/recovery). Heart rate reactivity was the parameter most often measured (13 studies), but only the initially low fit female students of Holmes & McGilley[255] showed a

decreased reactivity after training. One study reported a lower heart rate during the recovery phase after the tasks[38] , but in seven other studies no such effect was seen. In the study that reported better heart rate recovery, blood pressure also recovered more fully, but the finding was complicated by the fact that there were clear differences in recovery between the aerobic and control groups even before the start of the training. Of the ten other studies measuring blood pressure responses, only Sherwood et al.[511] reported a decrease in diastolic blood response in a subset of 5 borderline hypertensives. Furthermore, in the study of Helin & Hänninen[237] a clear *increase* in blood pressure reactivity was seen, rather than a decrease. With regard to the stress-hormones: the increases in plasma adrenaline and noradrenaline in response to stress were not reduced by training, and in one study post-stress levels in urine were even found to be higher (sic) after training.[113] From the measurement of all other parameters (EDR/SCL, EMG, CO, SV, RSA, PEP, RR, TPR) no consistent evidence for a beneficial effect of training emerged. Overall, stress-reactivity tended to decrease over time, but the decreases in the aerobic training groups were not stronger than the decreases in the alternative treatment groups or even in the waiting-list control groups. The conclusion from these studies therefore, should be that aerobic training does not reduce stress-reactivity over and above the spontaneous reductions that occur over time. Those few reports that did find specific advantages of aerobic training are offset by the two reports that reported higher reactivity after training.

Although the emphasis has been on aerobic endurance capacity, six studies also assessed the effect of anaerobic or strength training. These programs involve the use of high intensity short-duration muscle work, like the exercises of the Nautilus circuit, or the apparatus-oriented exercises usually found in commercial fitness centers (wrist curls, bench press, shoulder shrugs, leg raises, hamstring curls, leg press etc.). The strength training was used as a "placebo" treatment because it barely influences aerobic fitness. However, it is not impossible that these programs themselves are effective in reducing stress-reactivity, based on unknown physiological or pure psychological mechanisms. In that case, the failure to find differential effects of aerobic and strength training, would not preclude the possibility that training in general (be it aerobic or otherwise) reduces reactivity. The beneficial effect of aerobic training could even have been masked by an equally large beneficial effect of the strength training. Unfortunately, strength training in the above studies equally could not be shown to reduce stress-reactivity. Out of the many parameters measured in six studies, only diastolic blood pressure reactivity in one study[40] significantly decreased in response to strength training. In contrast, Sherwood et al.[511] reported increased cardiac β-adrenergic and stroke volume reactivity, and a greater fall in peripheral vascular resistance after strength training. In fact, the latter effects of strength training contributed strongly to the significant differences between the anaerobic and aerobic groups. The use of strength training therefore, did not mask an effect of aerobic training, but on the contrary inadvertently enhanced it. In conclusion, using anaerobic strength training as a control treatment is not likely to have prevented effects of aerobic training to show up. Both training forms were equally ineffective in changing stress-reactivity.

In spite of the failure to find a statistically reliable effect, several studies did report a tendency toward reduced cardiac β-adrenergic and diastolic blood pressure reactivity after aerobic training[511, 38] , as well as a faster plasma adrenaline recovery.[40] The authors explain the failure of the effects to reach statistical significance to the small group sizes and the short duration of the training programs. In particularly the latter, too short a duration of training programs, has been used by several authors as a post-hoc explanation for the failure of training to reduce stress-reactivity. Indeed, the 7 to 16 weeks of training of the first 13 studies may not have been sufficient to create the necessary physiological or psychological basis for reductions in stress-reactivity. However, recently, Albright et al.[4] found no effects on heart rate and blood pressure reactivity in a group of 83 men and women after of home-based walking and jogging for a period of six months. In the study detailed in chapter 6, 44 subjects received 4 months of training and 11 subjects received 8 months of supervised training, but neither training- to control-group comparisons, nor a direct correlation to the number of hours trained revealed an effect of training on reactivity. The failure to find training effects is not likely due to inadequate manipulation of aerobic power, since Vo_{2max} was significantly increased in both studies and no direct correlation was found between the individual improvement in Vo_{2max} and changes in reactivity over time. These results argue strongly against the notion that training of longer duration will show significant reductions in stress-reactivity. They do support the general conclusion from table 12 that training does not influence stress-reactivity.

It is possible that subjects may be more performance oriented after a program of exercise training, put in more effort when challenged, and consequently show higher physiological reactivity. Conversely, untrained subjects may, in competitive challenging situations, experience relatively more distress. This may lead them to reduce their attempts to effortfully cope with the task and subsequently lower their physiological responsiveness. Clearly, differences in distress, effort and performance are serious confounders when comparing the stress-reactions of control groups to trained groups. Self-report of subjective arousal and distress have been obtained in a number of studies.[523, 255, 237, 511, 554] Whether subjects were asked to report on cognitive arousal, somatic arousal, tension, concentration, anxiety, or effort spent on the tasks, no effects of training were found. Furthermore, several studies that measured objective task performance in terms of percentage correct and average reaction time failed to find any improvement after training ([511] , and chapter 5 and 6). There was one intriguing exception. In the only study to report *increases* in cardiovascular reactivity after training[237] , training also clearly improved observer ratings of a public lecture. Unfortunately, audio-cassette relaxation training improved teaching performance even more, although it significantly *reduced* stress-reactivity. Obviously, the increased reactivity after exercise training was not a necessary condition for an improvement in teaching performance. In general, the failure to decrease reactivity after training does not seem to be compensated by improved task performance.

Individual benefits

The failure to find effects of exercise on the average reactivity in an entire group of trainers does not preclude the existence of a subset of individuals who do reduce their stress-reactions in response to training. Identification of such individuals, and establishing by what they are characterized, seems a next logical research question. As had already been hypothesized in 1972 by Folkins et al.[178] , those who are in the poorest physical and psychological condition may benefit most from exercise programs. The former possibility, that only subjects with low initial fitness will reduce their reactivity in response to training, had already prompted several studies to specifically select untrained and/or low fit subjects. In spite of the low levels of initial fitness however, these studies yielded little evidence for reduced stress-reactivity. In addition, two studies directly related training-induced changes in fitness with changes in reactivity. This yielded only two significant correlations: Sinyor et al.[523] found a relation between the increase in Vo_{2max} and heart rate levels after 5 min of recovery, and in chapter 5 we found that subjects with the largest improvement in Vo_{2max} showed smaller decrements in vagal tone during stress. These seemingly related findings suggest that large increases in fitness cause a quicker parasympathetic mediated heart rate recovery after stress. However, neither faster heart rate recovery nor reduced vagal withdrawal could be replicated in our recent study (chapter 6), where individual differences in training effects ranged from 0.5 to 35 % increase in Vo_{2max}. Correlations of changes in Vo_{2max} after 4 or 8 months of training failed to relate to changes in reactivity of any of the variables measured. Apparently, low initial fitness and/or a relatively large training-induced increase in fitness do not improve the chances of finding a training effect on reactivity.

Apart from low levels of initial fitness and physical activity, an unfavorable psychological make-up and/or exaggerated physiological reactivity to stress may cause some subjects to benefit more from training than others. In chapter 6, changes in several psychological variables (e.g. anxiety, depression, anger, self esteem, vigor etc.) were assessed and brought into relation to changes in reactivity after 4 or 8 months of training. No relationships between the psychological and physiological training effects were seen at all. However, the latter finding was complicated by the fact that training caused little or no psychological effects. In short, the absence of psychophysiological training effects was coupled to the absence of psychological training effects. Indirectly, this suggests that profound changes in psychological make-up are needed before an effect on reactivity will be found. Five of the studies reviewed above deliberately used Type A's subjects, who are hypothesized to be at increased risk for coronary heart disease due to their behavioral style. In two of these studies the type A's were even specifically selected because they had shown to be physiologically hyperreactive to stress. Yet, fitness training failed to change either type A behavior or physiological stress-reactivity. Two studies that performed separate analyses on the most reactive subgroup also failed to find a specific effect of exercise training[4, 509] , and there was no direct relation between initial reactivity and the change induced by training (chapter 6). In general therefore, the hyperreactives are seen to remain hyperreactive following a fitness training program.

In conclusion, the present evidence refutes the suggestion that training influences the physiological stress-response. I have, exhaustively, tried post-hoc identification of factors that may have prevented the beneficial effects to show up, but duration of training, initial fitness/reactivity status, nor possible increases in effort and performance could change the overall negative conclusion. Table 12 further suggests that the conclusion holds independently of sex, social class, age, choice of stress-tasks or physiological variables. Of course, generalizability of the results is necesarily limited to members of the "normal" healthy work-force that volunteer for fitness programs. To date, the effects of exercise training on the physiological stress-reactivity of patients suffering from depression, anxiety, or job-related psychosomatic complaints have not been studied. Given the fact that beneficial psychological effects on mood and well-being may be limited to these groups[521] , training effects on stress-reactivity may also be confined to these subjects. Cardiac patients or youngsters with a parental history of hypertension form two other subgroups in which the effectiveness of training to reduce stress-reactivity has not been assessed, although they may be the ones who will experience the most direct advantage of low physiological arousal under stress. Definite answers on the effectiveness of training to tackle reactivity in these extreme groups will have to await the results of future studies. However, the lower stress-reactivity found in high fit exercisers compared to low fit sedentaries (see chapter 4) must have largely reflected differences in endowment for fitness and/or psychological make-up between these groups. Exercising per se will not reduce physiological stress-reactivity.

8.3. Re-evaluating the reactivity hypothesis

The above conclusion is very disappointing. It might discourage initiative in government and corporations alike to increase stress-resistance in their population/work-force by providing fitness programs. However, before dismissing aerobic training as "useless", let us reconsider some of the tacit assumptions underlying the research on stress and exercise so far. Starting point of most studies has been the finding that exercise reduces the risk for CHD, whereas stress increases this risk. Since the protective effect of exercise cannot be explained by the classical risk factors alone, an influence of exercise on the detrimental effect of stress seemed a highly attractive hypothesis. Up till now, I have been reasoning that exercise must directly interfere with the physiological response to stress. This expectation stemmed largely from the emphasis on exaggerated physiological reactivity as the cause of stress-related disease in current psychosomatic theory.[385] In this "reactivity-hypothesis", the stress-response is considered to have been adaptive only where it rapidly prepared the organism for fight or flight in moments of physical threat, i.e. in animals and primitive man. In contemporary Western society, where most threats are of a symbolic nature, repeated activation of the sympathetic nervous system may become harmful, rather than helpful. As Walter Cannon put it as early as 1929:

" ..if the state of extreme perturbation continues in uncontrolled possession of the organism for any considerable period, without the occurrence of physical activity, dire results may ensue..." (Cannon, 1929, p. 176).[74]

In the field of cardiovascular psychophysiology it has been widely assumed that

exaggerated stress-reactivity measured in the laboratory is a valid indicator of a tendency towards exaggerated reactivity in general, and that by measuring laboratory stress-reactivity we could index individual susceptibility to real-life stress. However, some doubts are starting to arise.

Reliability and consistency of stress-reactivity

The use of reactivity as a risk factor requires it to be a stable individual characteristic. Test-retest correlations of reactivity to commonly used tasks like mental arithmetic and video games over intervals of days to years suggest moderate reliability at best.[555, 451] Meta-analysis by Steptoe and Vögele[555] provided average coefficients on heart rate and blood pressure reactivity over 17 studies. The heart rate response was the most reliable (averaging 0.62), followed by systolic blood pressure (0.52) and diastolic blood pressure reactivity (0.30). Reliability of less studied variables like pre-ejection period, respiration rate, or peripheral resistance and cardiac output responses also varies between 0.15 and 0.63.[420, 159, 6] Perhaps the most striking finding is the large variation in reliability coefficients across studies. This may be due to differences in the task situation like novelty, motivation, controllability, skill, and task difficulty that exert a strong influence on reactivity. Controlling for these effects by standardization of the task situation and aggregating across trials and tasks may markedly improved reliability.[288] Eliminating novelty effects by repeated application of a stressor improves reliability even further. In the study reported in chapter 6, test-retest reliability of SBP/DBP reactivity from the first to the second measurement was only 0.34/0.41, but improved to 0.71/0.80 from the second to the third measurement. Similar improvements in reliability have been found by others in our laboratory (Willemsen & Westdorp, personal communication). Therefore, once the task is highly standardized and novelty effects are reduced, individual differences in physiological reactivity constitute a reliable individual characteristic. However, almost as a consequence of the above, the consistency of reactivity across task situations is highly unsatisfactory.

The correlations between heart rate and blood pressure reactions to different tasks presented in the same laboratory session are generally in the range of 0.3 to 0.7.[132] Although the responses to "psychological" tasks are more related to each other than to the response to physical tasks[440, 442, 188, 347, 288] , even within tasks that trigger "purely" psychological responses, intertask correlation of reactivity is low to moderate.[391, 188, 191, 347] This low intertask consistency is not necessarily due to low reliability. Within a two hour session, good reproducibility of the responses to mental arithmetic and a complex cognitive task was found (0.56 - 0.84), but the correlation of reactivity to these tasks was nil.[191] Perhaps we can identify a subset of "high reactors", by assessing an underlying physiological mechanism, rather than a single variable. Stressors that seem to trigger comparable increases in heart rate and blood pressure within the same individual, may in fact trigger totally different response patterns in terms of vascular versus cardiac reactivity, as was seen in chapter 5 and 6. A sophisticated cluster analysis using several different variables (HR, BP, PEP, RSA, SV, TPR) showed that only 9 out of 73 subjects responded systematically with β-adrenergic reactivity to a

reaction time task, mental arithmetic and the cold pressor test.[8] Four subjects were consistent α-reactors, and only 8 subjects were unresponsive with all variables to all tasks. The other 52 subjects did not respond with a consistent pattern to the different tasks. The question arises how many consistent reactors would have remained if still more other tasks had been added. Likely, this would have depended on task selection, since correspondence between reactivity to different tasks increases when the tasks are very much alike.[347, 288] Since the variety in behavioral stressors in real-life is much larger than in the laboratory, the low generalizability of reactivity may represent a more serious problem than low reliability. Therefore, the most crucial test of laboratory reactivity lies in its ability to predict the response to real-life stress.

Validity of stress-reactivity

Recent reviews of studies relating the responses to laboratory stressors with those to real-life stressors concluded that laboratory reactivity does not reflect reactivity in the field situation very well.[451, 132] Real-life stress-reactivity has been defined in various ways. Some studies have used the increase in the levels of heart rate and blood pressure from rest to work, or from sleep to awake, as an index of reactivity.[144, 232, 329] Others used variability indices, like the standard deviation, or the mean square successive difference of readings throughout the day, or periods of the day.[540, 457] Intra-arterial recording of blood pressure even allowed the scoring of blood pressure variability on a beat to beat basis.[173, 440] None of these real-life reactivity measures were more than weakly related to laboratory stress-reactivity (best correlations HR: 0.31[457] BP: 0.53[173]), and often no significant correlation was found at all. However, as Pickering and Gerin[451] justly point out that, there is little reason to expect very high correlations between mental stress testing and day-time cardiovascular variability. Most of the variation in heart rate and blood pressure is created by physical activity and postural changes, rather than psychological challenges. Indeed, laboratory challenges without a behavioral component (cold pressor, exercise) were generally not worse predictors of ambulatory reactivity and variability than mental stress testing.[451] From a psychosomatic stance, the important question is whether laboratory reactivity predicts the response to real-life stressors of a psychological nature. To answer this question, various studies have looked at the cardiovascular and hormonal response to real-life stressors like an exam[601, 131] or a public speech.[118, 585] Again, correlation of reactivity to the laboratory tasks and the real-life stressors rarely exceeded the .50 level.

Even if ambulatory variability or the reactivity to specific real-life stressors cannot be reliably predicted, then laboratory reactivity may still be useful to predict the overall levels of cardiovascular and hormonal activation throughout the day. These levels may reflect the accumulative effects of various natural stressors, rather than the response to one or more specific stressors. Unfortunately, ambulatory monitoring studies have refuted this idea. Only a weak relationship was found between laboratory reactivity and daily heart rate and blood pressure levels.[144, 404, 232, 189, 540, 268, 202, 286] In fact, the best correspondence between laboratory and ambulatory data is found when absolute levels of blood pressure and heart rate during the day are predicted from the absolute task

levels, rather than reactivity.[391, 202, 404, 232, 189, 268, 329] However, task levels depend strongly on the resting level, and the prediction of ambulatory levels from task level is indeed not much better than from resting levels alone.[391, 404, 232, 268, 329] Once the resting level is known, there seems to be no additional gain from (laboriously) measuring the response to stress. This is quite surprising because ambulatory levels of blood pressure predict hypertensive complications better than resting levels.[533, 110, 464] Apparently, there is a (stress-related?) increase in daily heart rate and blood pressure that is not well predicted by short-term reactivity to specific stressors or even the overall levels during laboratory stress testing.

The low predictive validity of laboratory reactivity has been attributed to various methodological problems. Particularly the choice of an adequate baseline (e.g. sleeping level or separate day) may enhance the laboratory to real-life correlation, since it reduces the dependency of laboratory reactivity on individual differences in "test-anxiety".[457] In addition, many of the ambulatory monitoring studies were hampered by inadequate seperation of physical (posture, activity, sleep-wakefulness cycle), metabolic (ambient temperature, smoking, eating, coffee) and behavioral influences. This may have led to an underestimation of the predictive power of laboratory reactivity. Finally, it has been proposed that laboratory and real-life responses may reflect a common physiological mechanism (e.g α-adrenergic hypersensitivity) that cannot be measured by one task or one variable only.[132] However, the use of sleep as a baseline or thorough correction for the effects of physical activity and posture did not lift the correlation between laboratory and real-life reactivity to acceptable levels.[278, 457] Furthermore, a study using multiple laboratory tasks, as well as extensive measurement of the hemodynamic response pattern (e.g. cardiac output and total peripheral resistance) still did not predict real-life levels very well.[131] Therefore, researchers must face the possibility that the low predictive power of laboratory reactivity is not only due to methodological problems, but also to its low construct validity.

During most of the laboratory tasks, the changes in autonomic nervous system activity are short in nature and reflect the effort of the subject to perform well on the task. Recovery from these tasks is often rapid and the majority of subjects will have returned to baseline physiology by the end of the experimental session. Due to the short duration of the tasks and the voluntary nature of stress-testing, one may doubt whether subjects ever experience the kind threat encountered in real-life stress. In real life, exposure to stress triggers behavioral and emotional coping mechanisms by which the subject tries to deal with the stressor.[334] Succesful coping will enhance rapid recovery to baseline physiology and may prevent the same situation to evoke a stress response the next time. Failure to cope with stress on the other hand may convict the subject to sustained physiological activation. In that case, repeated exposure will no longer lead to rapid habituation, and anticipatory physiological activation may begin already far before the actual exposure to stress. To complicate matters this coping with real life stressors is an ongoing process. A problem that has been successfully mastered at one time may still become threatening at another when performance fails, or adequate social support is suddenly lacking. Therefore, even the response to real-life stress itself may not show high stability over time. Clearly, the complex coping mechanisms used to deal with real life stressors

can hardly be expected to be predicted from laboratory stressors.

Perhaps even more serious than doubts about the reliability and validity of laboratory reactivity is the fact that reactivity per se may not be relevant to later disease at all. At present there is only meager prospective evidence in humans linking exaggerated heart rate reactivity to laboratory stress to coronary heart disease.[374] In fact, high heart reactivity to mental stress[182, 3] , as well as high ambulatory heart rate variability[309, 101] , were both found to be associated with *lower* risk for coronary heart disease. The reactivity hypothesis appears to do slightly better in hypertension. Several prospective studies showed hyperreactivity to exercise testing[367, 443] , the cold pressor test[396] , or mental stress testing[162, 44, 416] to precede an increase in casual blood pressure. Furthermore, borderline hypertensives[550] and children from families with a positive history of hypertension[161, 421, 9, 401] are more reactive to stress than their counterparts, even before hypertension has set in. This could be taken to mean that high reactivity to behavioral stress by itself causes hypertension. However, subjects with a positive family history (FH+) of hypertension may have a number of characteristics that cause both hypertension as well as hyperreactivity, e.g. low baroreflex sensitivity[92, 123] , or impaired vasodilator capacity secondary to membrane transport defect.[44] Inclusion of such subjects in prospective population studies may inadvertedly have suggested that high reactivity precedes (and thus causes) hypertension.

A two-stage model of reactivity

Although the translations of the complex links between stress and disease into measurable research questions is essential to scientific progress, laboratory stress-reactivity (often limited to the heart rate response only) has acquired an almost divine status in cardiovascular psychophysiology. At present however, it fails to meet the demands of predictive, construct, and ecological validity that are required to use it as a risk factor for CVD. This does **not** refute the idea that behavioral factors play an important role in CVD and that the physiological stress-response stands at the basis of such stress-induced disease. The time scale of the physiological responses may be all important. So far, research has concentrated on the response amplitude during short-term stress, rather than looking at the dynamics of the stress response over a prolonged period of time. Since there are striking individual differences in acute stress-reactivity and since the sometimes fierce reactions were so clearly unjustified in metabolic terms, hyperreactivity had a high face validity as an individual risk factor for CVD. Ease of measurement may have played a further role, since little laboratory resources are needed to measure heart rate and blood pressure after the subject is ordered to perform three-digit additions or subtractions. Note however, that even Cannon spoke of "extreme perturbations" for "any considerable period" rather than 10 minutes of mental arithmetic or a 2 minutes cold pressor test. Only when stress is frequent and prolonged, without the opportunity to full recovery, the physiological overactivation may result in disregulation of cardiovascular control mechanisms and tissue damage. Individual differences in susceptibility to stress-induced disease may not be found in the acute alarm reactions, lasting only minutes to hours. Instead, the crucial link between stress and disease may lie in subsequent

processes of adaptation or exhaustion that take up days, months or even years.

The animal studies of Henry et al.[240] provide an example of the two-stage nature of stress. They have shown that the initial defense reaction to stress, associated mainly with catecholamine and cardiac β-adrenergic reactivity, gradually gives way to passive, immobile helplessness, with vagal activation and pituitary-adrenocortical responses. Only the latter responses will lead to disease, e.g. in the form of ulceration and hypertension. This two-stage model was in close accordance Selye's original formulation of the general adaptation syndrome. According to Selye, stress causes an acute alarm reaction that helps the organism to adapt to the stressor at hand. Without appropriate unwinding however, the "adaptive energy" may get depleted, leading to exhaustion and finally disease. Selye's ideas have been criticized for lack of a biological pendant of adaptive energy. However, the shift from catecholamine responses to cortisol proposed by Henry et al.[240] could provide a plausible biological basis for the gradual exhaustion on prolonged exposure to stress. Furthermore, there is evidence for a gradual loss of adaptation within the pituitary-corticoadrenal response itself, if stress is prolonged. ACTH-triggered cortisol release is normally inhibited by cortisol action on the pituitary gland. This negative feedback loop loses its effectiveness after chronic stress, because the hypophyseal receptors lose their sensitivity to cortisol.[310] As a consequence, prolonged increases in cortisol tend to further slow recovery of the cortisol to stress.

Recently, Siegrist et al.[517] have proposed a two-stage model of reactivity during adult life on an even larger time scale. The first stage, in early career, is defined by pronounced reactivity following exposure to challenge: the subsequent stage is characterized by reduced maximal responsiveness under challenge, reflecting chronic arousal and exhaustive coping. In their model, low cardiovascular reactivity observed during effort and struggle is not considered to reflect stress-resistance, but, on the contrary, a loss of functional capacity to deal with stress. Again, exhaustion is crucial to disease, not reactivity. The model is well compatible with theories linking personality characteristics (type A, hostility) to coronary heart disease. Hard driving, hostility, excessive commitment, suppression of fatigue, and a strong need for control over one's situation contribute to frequent and prolonged efforts to master the environment, and thus predispose to exhaustion.[208] Preliminary evidence for a two-stage model came from a study where subjects with high work demand and low control over one's occupational status (job security, risk of downward mobility, inability to promote) had the lowest heart rate and blood pressure reactivity at the end of a work-day.[518] However, in spite of their low stress-reactivity, subjects with high occupational stress have increased risk for CHD.[519]

Siegrist et al.[517] have suggested that exhaustion is reflected at the biological level in down-regulation of the adrenoceptors. It is known that in response to adrenaline infusion there is a brief increase in the number and sensitivity of adrenoceptors during the first 30 minutes followed by a functional down-regulation, even below the basal levels, if infusion is prolonged up to several hours. This suggests that repeated increases in plasma adrenaline during prolonged stress could lead to impaired β-2-receptor functioning. In rats, restraint stress was indeed seen to cause a decrease in the lymphocyte β-2-receptor number[36] and sensitivity[576] , and foot shock was seen to reduce atrial responsiveness

to noradrenaline.[21] Mental stress in humans evokes an acute increase in the number of β-2-receptors, and this is entirely due to the increase in plasma adrenaline.[213, 214] It is possible that longer stress might result in a similar down-regulation as seen in the adrenaline infusion studies. Unfortunately, only brief periods of stress were studied, and there is at present no information on the effects on β-receptor function during longer term exposure to mental stress. However, depressed patients have less β-2-receptors on leukocytes than normal controls[439] , and chronic treatment with β-2-agonists leads to a reduction in β-receptor responsiveness[384] , which is compatible with the idea that long-lasting psychological stress leads to an impairment of β-receptor functioning. In addition, a gradual reduction in β-receptor sensitivity could indeed explain the loss cardiovascular reactivity after chronic stress seen by Siegrist et al.[517] Heart rate reactivity to mental stress was seen to depend largely on individual differences in adrenergic sensitivity of the heart[145] and was highly related to resting β-receptor density and sensitivity on lymphocytes.[402]

Hyperreactivity and fitness

The re-evaluation of stress-reactivity is taken even one step further by Dienstbier, who considers it to be a normal sign of adaptive coping.[114, 115] Contrary to the present research paradigm, he expects catecholamine reactivity to stress to become higher as a consequence of exercise training, rather than lower. Various manipulations in young animals, including intermittent shocking, loud noises, handling, cold stress and rearing with another species led to emotionally stable adult animals. Most behavioral therapy in humans too, is based on repeated exposure of patients to the very situations which cause them stress, until they become habituated and impervious to it. Therefore, it is thought that repeated exposure to stress and its physiological consequences leads to the acquisition of what has been termed "stress-tolerance"[216] , "mental hardiness"[314] , or "physiological toughness".[114] Such toughness can be brought about by intermittent exposure to manageable challenge/threat situations, provided there is adequate time to recover. Psychosocial stress may not often meet the last requirement, but exercise is seen as a well-demarcated, but physiologically potent stressor, that may precipitate tolerance to stress in general. In its theory, this idea hinges a little on traditional views of exercise (and cold showers) as a way to induce masculinity, but animal research has given it a good empirical basis. The main physiological correlate for stress tolerance is increased resistance against central noradrenaline depletion, and increased ability to maintain high peripheral catecholamine reaction in the face of stress. Indeed, habituation of the catecholamine response to a familiar aversive stressor in animals gives enhanced, rather than decreased potential for an exaggerated SNS response to novel stressors.[321, 389] This suggests that high catecholamine reactivity is essential to successful coping, particularly in confrontations with novel or severe stressors. The view of the physiological stress-reactions as a necessity, rather than a nuisance, corresponds to popular notions of adrenaline as being essential to good performance. In humans, catecholamine responsivity to stressors (laboratory tasks, exam, anticipating a parachute jump) has in fact repeatedly been associated with good performance, particularly in males.[587, 467, 184]

In addition, catecholamine reactivity to stress was largest in subjects scoring high on emotional stability,[587, 467] a fact borne out by our own study (chapter 6).

If high adrenergic responsivity is adaptive, then well-trained subjects should have a clear advantage over untrained subjects. One of the characteristic features of well-trained subjects is the enhanced substrate mobilization in response to exercise. Apart from the increased secretory capacity of the "sports adrenal medulla"[306, 305] , the target cells are more responsive to adrenaline, possibly through increased sensitivity of the β-receptors.[382, 564, 361] As a consequence adrenaline induced glucose and FFA mobilization is larger in the high fit.[99, 306] Based on the increased potential for adrenergic reactivity, Dienstbier predicts a pattern, whereby fit subjects have high catecholamine reactivity to (novel) tasks requiring high effort, but show low reactivity to mild stressors, greater adaptation over repeated exposure to the same stressor, and lower basal levels of adrenergic tone in general.[114] The lower overall level of catecholamines will guarantee cardiovascular health and can easily overcome the effects of increased catecholamine reactivity during acute stress. Exercise is also thought to decrease the base levels of cortisol and to postpone cortisol responses to stress, since cortisol reflects distress and and exhaustion, and is associated with poor performance.[587] This clearly links the toughness concept with the two-stage models of reactivity. Training-induced toughness and exhaustion after chronic stress can be seen as the poles of a continuum defined in terms of high adrenergic sensitivity and low pituitary-adrenocortical action versus low adrenergic sensitivity and high pituitary-adrenocortical action.

Do the cardiovascular effects of fitness training fit the alternative models?

Since cardiovascular reactivity expresses effort more than distress, the various ideas presented above would lead us to predict a different outcome of fitness training than a mere reduction in reactivity. Fitness training should leave cardiovascular reactivity to severe and novel stress unchanged, or even enhance it, preferably in combination with improvements in performance. Only on repeated exposure to stress, or when little effort is needed, reactivity may be lower. In any case, the overall level of heart rate and blood pressure should be lower after training. The latter is supported by virtually all of the cross-sectional studies reviewed in chapter 4, where high fit exercisers had lower levels of heart rate and diastolic blood pressure under stress. In the majority of these studies the lower stress levels were based on lower resting levels. In about half of studies the effect was strengthened by either a lower heart rate or a lower blood pressure reactivity in the high fit exercisers. Only two cross-sectional studies, suggested higher blood pressure reactivity in subjects with the highest aerobic fitness level (see chapter 6). Both studies were characterized by highly involving and effort demanding tasks. It is noteworthy that, in spite of high blood pressure reactivity, blood pressure levels during stress in both studies were not higher in the high fit in comparison to the low fit, because the high fit had lower resting levels. The longitudinal studies are perhaps best summarized by the results in chapter 6. After training there is unchanged reactivity and overall levels of heart rate and diastolic blood pressure are lower. Interestingly, the only study to report increased diastolic and systolic blood pressure reactivity after training was also the only study to

use a potent real-life stressor, i.e. lecturing in public. In spite of the increased reactivity during the lecture, resting levels of both systolic and diastolic blood pressure were clearly decreased after training.[237]

I have repeatedly argued that, with regard to disease, a reduction in levels is far more important than a reduction in reactivity. Clearly, the two-stage models agree on this, since average heart rate and blood pressure level throughout the day reflect chronic stress much better than short-term increases in these parameters, that may merely reflect task-related effort. Various other findings support the idea that levels rather than reactivity are relevant to disease processes in CVD. For instance, antihypertensive therapy presents an interesting parallell to fitness training. Benzodiazepines, β-adrenoceptor blockers, and α_2-adrenoceptor agonists all share the property of reducing blood pressure in man and animal, but none reduces the acute pressor responses to stress.[209] In population samples, only resting or average daily blood pressure levels were found to be associated with incipient signs of cardiac and vascular hypertrophy, whereas neither blood pressor reactivity to mental stress,[286] nor ambulatory variability were associated with these hypertensive complications.[464] In monkeys, telemetrical recording showed that high levels of ambulatory heart rate clearly predisposed to coronary artery sclerosis, and the effect was independent of the acute heart rate response to the stress.[295] In short, a training-induced reduction in basal heart rate and blood pressure level without a change in reactivity should be neither surprising, nor worrisome, as long as the resulting stress levels are lower.

Applying the toughness concept to cardiovascular reactivity, we would predict that the high fit have the strongest reduction in the stress-response on repeated exposure to the same stressors. Some evidence for superior adaptation to stress in the high fit comes from a study by Claytor.[89] During presentation of novel stressors, being aerobically fit was not an advantage, but after repeated exposure, the fit subjects decreased their blood pressure responsiveness to the, now familiar, stressors more than unfit subjects. Also, the only two studies reporting lower noradrenaline reactivity in high fit subjects used a well-learned task, rather than a novel stimulus, and found the lower reactivity only during the latter stages of the stress protocol.[538, 539] Among novice teachers, the more fit subjects showed the strongest adaptation of the heart rate reaction to public speeching.[260] Blumenthal et al. reported equal blood pressure reactivity to the first two stressors presented (MA and speeching) before and after training, but lower systolic reactivity to the last stressor (video game).[41] In our own study (chapter 6), the higher reactivity in the more fit subjects was present only at the first confrontation with the stressors. Reactivity no longer correlated to fitness on repeated measurement after 4 and 8 months. During these final two sessions, stress levels of heart rate and blood pressure were significantly lower in the more fit subjects.

A final question is whether fitness training enhances task performance under stress, possibly in combination with higher reactivity. This issue has received relatively little attention. Only 6 out of the 30 cross-sectional studies reviewed in chapter 4,[522, 448, 513, 538, 343, 130] and only 4 out of the 15 training studies in chapter 8.2 gave performance data. Neither cross-sectional nor longitudinal studies suggested that (high fit) exercisers performed better on the mental tasks than the (low fit) sedentaries. However,

tasks in cardiovascular psychophysiology are often chosen to evoke substantial stress responses, and no effort is made to account for task difficulty, strategy, individual learning curves etc. Performance indices are limited to the number of errors and reaction times. Unfortunately, studies in human performance laboratory, that often use far more sophisticated measurement of cognitive function, have concentrated on the training effects on cognitive performance during strenuous physical load, rather than emotional stress.[575, 85] The only exception to this was a study of Sothmann et al.[539] , who showed that anagram performance time deteriorated after a double conflict task in low fit sedentaries, whereas high fit exercisers showed no such performance loss. Does physical endurance breed mental endurance? If so, the nature of such mental endurance is unclear. The cognitive skills of fit subjects may deteriorate slower during effortful coping (e.g less cognitive fatigue through better glucose transport). Alternatively, exercisers may simply be able to uphold performance motivation longer than non-exercisers.

Admittedly, the effects of fitness (training) do not seem to fit the alternative reactivity models much better than the classical reactivity hypothesis. However, virtually none of the research was aimed to test the physiological response during prolonged and severe distress, or the adaptation of the stress response on repeated exposure. Furthermore, only few studies have accounted for the possible confounding effects of effort and performance, and not a single study has measured the effects of fitness training on cortisol reactions to psychological stress. Instead, we have concentrated on cardiovascular reactivity to short-lasting laboratory tasks that were deliberately designed to evoke effortful coping. The ideas presented in this chapter suggest that such emphasis on short-term cardiovascular reactivity may not have been justified. Reactivity may lack the consistency and validity that are needed to use it as a meaningful individual trait. Furthermore, it may be far less plausible as a cardiovascular risk factor than heretofore thought, up to a point where high reactivity may even be regarded as a sign of health.

8.4. Exercise and stress: opposing effects on cardiovascular disease

To date, no prospective epidemiological study has tested a direct interaction between the effects of stress and exercise on the risk for cardiovascular disease. Such a study would need to test whether regular exercisers with high levels of work-stress show a reduction in mortality and morbidity over and above that seen in regular exercisers with low work-stress. It could well be that the beneficial effect of exercise and the detrimental effects of stress on cardiovascular disease are completely independent. The effects of stress and exercise would then simply be additive, rather than interactive, and exercise would be "merely" compensating the effects of stress, rather than preventing them. Put otherwise, people who don't experience stress might benefit from exercise as much as highly stressed people. In retrospect, it is unfortunate that the research on an interaction between stress and exercise has used the top-down approach characteristic of recent cardiovascular psychophysiology. That is, it tried to link individual differences in training state and fitness via stress-reactivity to pathology. This undertaking has clearly been without avail, and seems to support the idea that no interaction exists. In fact, so much was concluded in chapter 6. However, this conclusion may have been premature

particularly in the light of chapter 8.3. For the future, I propose to use a bottom-up approach. Starting point of our research efforts must be cardiovascular pathology itself. The important question to ask is how known or suspected risk factors are affected by chronic stress, and how they are affected by regular exercise. Only when these effects are known (and their mechanism understood), will it be sensible to look for a direct interaction of exercise and stress. Below I will venture an exploration of several mechanisms that may play an important role in coronary artery disease and hypertension. At the outset it is hypothesized that regular exercise systematically opposes the effects of chronic stress on these risk parameters. Furthermore, some evidence will be presented on physiological pathways for a direct interaction between the effects of stress and exercise, that could suggest that people suffering from stress may benefit even more from exercise than others. It is hoped that the remainder of this section will provide useful clues on how to direct our future research.

Coronary blood flow

Both heart rate and blood pressure levels are acknowledged risk factors for coronary heart disease. High blood pressure has long been thought to promote atherosclerosis by causing endothelial injury through increases in the shear stress at the vessel wall. Indeed atherosclerotic lesions tend to develop at sites of high turbulence in the blood flow (e.g. bifurcations). However, recent evidence suggests that most atherosclerotic plaques develop in areas with slow circulating blood flow that are opposite of sites with high wall stress.[377] It has been hypothesized that platelets and red cells are damaged or destroyed going through areas of high shear stress, and subsequently release their contents (ADP, platelet derived growth factor, serotonin, adrenaline) into the opposite areas with circulating blood flow currents. The platelets' contents may promote smooth muscle cell migration and LDL uptake by macrophages, and in established atherosclerosis, platelet thrombi are crucial in the final occlusion of the vessel lumen. Some wash-out of these platelet release products occurs during diastole, but only if heart rate is not too high, since high heart rates yield low, and even reversed, coronary arterial blood flow. Therefore, atherosclerotic lesion formation in the coronary artery may be directly coupled to absolute heart rate level.[24] Taken the clear rise in heart rate and blood pressure level during the work-day, and the raise in these parameters during prolonged psychosocial stress[578] , a joint change in coronary blood flow and pressure-related platelet damage may be a major mechanism by which stress causes coronary heart disease.

In contrast to chronic stress, regular exercise, by lowering the overall heart rate level, may increase total time spent in diastole, when changes in the rate of flow and departures from laminar unidirectional flow are least. This becomes especially advantageous under stress, when both blood pressure and heart rate rise, and blood flow is compromised the most. Chapter 6 provided direct evidence that regular exercise may lead to lower levels of heart rate and diastolic blood pressure, both at rest and under stress. However, some caution is in order. As discussed in chapter 8.3, the levels measured during laboratory testing are only imperfect indicators of the average levels of heart rate and blood pressure throughout the day. The advantages of training would be more

convincing if a direct effect could be shown with ambulatory monitoring. Unfortunately, training studies using ambulatory monitoring are far more scarce than training studies measuring resting or stress levels in the laboratory. Two out of the five studies known to me did not find a reduction in ambulatory diastolic or systolic blood pressure level after 16 weeks of intensive training in middle-aged hypertensives.[204, 41] Moderate intensity training did reduce ambulatory blood pressure level in older hypertensive subjects in a study of Seals & Reiling[505] , but the effects were very small. Better results were found by Somers et al.[534] who, in a combined training/de-training design, found a mean difference of 4.8/7.5 mmHg between the trained and the un- or de-trained states in borderline hypertensives. The decrease in blood pressure was limited to the day-time samples. In young and middle-aged normotensives, van Hoof et al. found a 5 mmHg reduction in DBP after 4 months of training, that was present during day-time only.[256]

A serious problem with the interpretation of these ambulatory studies is that they did not try to correct the ambulatory recordings for daily activity. Although little information is available on training effects on daily activity patterns, it is not unlikely that the increase in physical endurance and/or the participation in regular exercise may lead to a more active lifestyle (walking, biking and climbing stairs rather than using elevator and car), which will severely affect daily levels of heart rate and blood pressure. Perhaps training systematically reduces the blood pressure in specific situations, e.g. at rest and during cognitive and emotional load, without reducing the overall 24-hour level because of an increase in physical activity. The obvious question comes to mind whether an activity-induced increase in heart rate and blood pressure affects coronary blood flow in the same way as behavioral stress. It is, for instance, possible that circulating metabolites cause coronary vasodilation, while the exercise-induced increase in fibrinolysis neutralizes platelet action. Future research therefore, must try to combine ambulatory monitoring with detailed classification of daily activity. It is highly encouraging that, in spite of the incomplete activity recording, four of the five ambulatory studies have reported a significant decrease in heart rate level throughout the 24-hour recording period[256, 534, 505, 204] , that was reverted by de-training.[534] Therefore, coronary blood flow may form a first clear example of the opposite effects of chronic stress and regular exercise.

Cardiac autonomic balance

The reduction in the resting heart rate hints at a further mechanism by which exercise can counter the effects of stress. Training bradycardia may reflect a shift in cardiac autonomic balance, such that parasympathetic drive and sensitivity to its main neurotransmitter, acetylcholine, are increased, whereas sympathetic drive and the sensitivity to the catecholamines is decreased. The idea that exercise favors parasympathetic influences on the heart over sympathetic influences has direct bearing on its possible protection against sudden death, particularly during stress. Emotional upheaval has been long known to increase the chance of ventricular arrhythmias in animal and in man, and this may be largely due to a predominance of sympathetic over the parasympathetic nervous system.[355, 593] Pharmacological or surgical ablation of the sympathetic response to behavioral stress protects against electrical instability of the heart,[355] and a similar

protection occurs when parasympathetic nervous system activity is increased, e.g. by digitalis glycosides.[593] The protective effect of vagal tone appears to be particularly pronounced during, or perhaps even entirely limited to, periods of increased cardiac sympathetic drive.[593] In short, a training-induced increase in vagal tone, preferably one that remains intact during stress, could be an important factor in the lower sudden death risk of exercisers.

Unfortunately, the training-induced bradycardia, already called enigmatic in Scheuer and Tipton's 1977 review[494] , remains an enigma till the present day. Invasive (cardiac noradrenaline spillover) and non-invasive (PEP) indices of cardiac sympathetic drive were not different in trained and untrained subjects at rest,[398, 343, 564, 130] , or after adrenaline infusion.[564] Furthermore, chapter 5 and 6 showed that aerobic fitness training does not change resting PEP, and this was also found in the studies of others.[511, 564] Whether chronotropic sensitivity for β-agonists is altered by training remains unclear. Several studies show unchanged heart rate responses to isoproterenol[612, 335] and adrenaline[370, 382, 564] after training, but two studies reported a smaller isoproterenol-induced increase in heart rate.[565, 112] Likewise, animal studies suggest either unchanged cardiac β-receptor density and affinity[563] or a reduction in the density of the cardiac β-receptors.[229, 566] Training does cause a stronger increase in systolic blood pressure and cardiac output in response to β-agonists[318, 370, 564] , but it is unclear whether this reflects the increased stroke volume[564] or a stronger inotropic response.[543] In short, there is no consistent evidence for a reduction in cardiac adrenergic drive or adrenergic sensitivity after training. Furthermore, since the reduction in heart rate also occurs when cardioselective β-blockade is given during the training period, changes in cardiac β-adrenergic tone may not be crucial to the development of training-induced bradycardia.[427]

In rat studies, it could be shown that atrial content of acetylcholine, the neurotransmitter of the vagal nerve, was increased after training.[574] In response to sympathetic blockade, resting heart rate of well-trained human subjects increased more than that of untrained subjects.[193, 530] Furthermore, RSA, a non-invasive index of vagal tone, showed significant cross-sectional correlation with aerobic fitness[299] , and after training both RSA[438] , and RR variability were found to be increased.[504] However, various other studies cast doubt on the contribution of the vagus to training bradycardia. Both cross-sectional and longitudinal studies failed to support the findings of a larger heart rate increase after parasympathetic blockade in the trained state, or an increase in RSA.[297, 364, 503] In our own studies, resting RSA showed no cross-sectional relation to Vo_{2max}, and training did not result in increased RSA, in spite of the fact that overall heart rate was lower in the more fit and decreased in response to training. In the first study, we found evidence of smaller stress-induced vagal withdrawal in the more fit subjects, but the smaller RSA decrease was not related to a smaller heart rate response to stress. Furthermore, the RSA effect was not replicated in the second study. Therefore, our studies provided little evidence for an effect on vagal tone at rest or during stress. The lower overall heart rates in our fit and trained subjects must have mainly reflected a decrease in intrinsic heart rate. In fact, a decrease in the intrinsic heart rate, i.e. the heart rate obtained after complete removal of autonomic influences, appears to be the most

consistent observation in the studies on training-bradycardia.[195, 611, 297, 426, 530] Clearly, the lack of evidence for a beneficial training effect on the cardiac autonomic balance leaves unchanged the fact that this lowering of the intrinsic heart rate will lead to lower levels of heart rate under stress, with a concomitant improvement of coronary blood flow.

Baroreflex sensitivity

Does exercise also merely compensate the effects of stress on blood pressure? Evidence to the contrary comes from studies with spontaneously hypertensive rats, where fitness training stopped the onset of hypertension in animals regularly exposed to electric tail-shock stress.[95] The mechanism behind such a direct interaction is unclear, but the baroreflex could be implicated. Abnormalities in baroreflex function in both animal[1, 356] and human hypertension have been demonstrated in numerous studies, with hypertensive subjects exhibiting diminished baroreflex sensitivity compared with their normotensive counterparts.[142, 604, 174, 441] Whereas the impairment in the baroreflex was initially attributed to reduced arterial distensibility, secondary to the elevated pressure itself, recent studies suggest that the abnormality can precede the onset of hypertension.[444] It has been hypothesized that a low baroreflex sensitivity is particularly inadequate during stress, because it enhances blood pressure reactivity, and by way of that the risk for hypertension.[123] Improvement of the baroreflex sensitivity by training therefore, might play an important role in the antihypertensive effect of exercise, and provide a pathway for a direct interaction between stress and exercise. Unfortunately, even after a multitude of studies in this area, the precise effects of exercise on the baroreflex remain a mystery. In both animals and man, the trained state has been associated with decreased[544, 23, 225, 565, 529, 304] increased[419, 20] or unchanged carotid baroreflex sensitivity.[503, 504, 597, 344, 339] A similar discrepancy in results is found for the sympathetic effects on blood flow through splanchnic, renal and muscular vessels. During lower body negative pressure training has been found to reduce vasoconstriction[597, 504, 365, 339] , and to predispose to syncope in some studies[447] , although others report unchanged reflex vasoconstriction.[344, 506] Although detailed interpretation of these studies is beyond the scope of this thesis, one interesting point should be noted: Equivocal results have been limited to normotensives, whereas studies using hypertensive patients consistently report increased carotid baroreflex sensitivity with training.[534, 438] Perhaps an impaired reflex control (due to a low vagal tone?) is needed before training is effective. On the other hand, the restored baroreflex sensitivity after training in hypertensives may be secondary to blood pressure normalization.

Recently, a highly elegant experiment of Anderson et al.[10] showed that the blood pressure response as well as the muscle sympathetic nerve response to stress was not diminished when the baroreflex sensitivity was impaired by phenylepinephrine infusion. This suggests that a change in the baroreflex sensitivity is not the cause of the increase in blood pressure increase during stress, but merely follows it. That could also explain the apparent contradiction in chapters 5 and 6, with regard to the association of fitness with diastolic blood pressure and RSA reactivity. In chapter 5 the lower diastolic blood

pressure response of the more fit was paired to a smaller reduction in vagal tone. In chapter 6, diastolic blood pressure reactivity was higher in the more fit, and vagal withdrawal in response to stress was no longer related to fitness. In the latter study, the higher (effort-related?) diastolic blood pressure reactivity in the more fit possibly dictated a loosening of baroreflex control over the heart rate, leading to a reduction in vagal tone. It may be surprising that this reduction in vagal tone was equal to, and not larger than that in the less fit subjects, although that might have been predicted on the basis of the greater blood pressure reaction. However, in the more fit, a similar increase in heart rate may yield greater cardiac output effects because of the larger stroke volume. The main point to make is that, even if baroreflex sensitivity is larger in trained subjects, this is not likely to cause lower blood pressure reactivity to stress.

Adrenoceptor sensitivity

Since hypertension is characterized by an increase in sympathetic activity, with concomitant rises in plasma levels of noradrenaline and adrenaline[82] , training could counter hypertension by reducing the plasma catecholamine level. However, the bulk of training studies suggest that the resting plasma level of noradrenaline is generally unchanged after training (reviewed in Sothmann[539]), and only subjects with high initial noradrenaline levels show reduced basal noradrenaline after training. Furthermore, muscle sympathetic activity, directly measured from the peroneal nerve, was not found to differ in exercisers and non-exercisers, and[506] radiotracer studies disagree on noradrenaline appearance rates, although they agree on unchanged noradrenaline clearance after training.[456, 398] Likewise, basal adrenaline level is generally reported to be unchanged after training, and well-trained subjects tend to have even slightly higher resting values than untrained subjects.[563, 306, 280] In short, there is little evidence to suggest that training counteracts hypertension by reducing sympathetic nervous system output. However, the action of the catecholamines is largely determined by their effect on the adrenoceptors. Several lines of evidence have collided to suggest that the relationships between stress, exercise and hypertension may be critically dependent on β-receptor functioning.

At the outset, hypertension is characterized by increased cardiac output. After some time cardiac output normalizes, but the blood pressure is kept high by an increase in peripheral resistance. The change from increased cardiac output to increased vascular resistance has been hypothesized to reflect a shift in sympathetic nervous system output from the heart to the vessels, secondary to dysfunction of central regulatory mechanisms[285] or to reflect gradual changes in vascular morphology, secondary to an increase in blood pressure[180] or tissue overperfusion.[429] There is however, another explanation that accounts for the shift in cardiovascular pattern. This explanation holds that a gradual increase in basal sympathoadrenal tone in the early stages of hypertension is accompanied by a selective desensitization of β-receptors with the development of a concomitant unopposed dominance of α-adrenergic receptor functions.[82] In agreement with this, many studies have reported that the gradual lowering of cardiac output is coupled to a reduction in cardiac β-receptor sensitivity[16, 166] which may be its very cause. More importantly, reduced β-2-receptor sensitivity in the vessels would favor vasoconstriction

over vasodilation which could explain the gradual increase in vascular resistance. Brodde et al. sugested that hypertension is associated with an impairment of the β-adrenoceptor/adenylate cyclase system, such that basal receptor density and sensitivity may be high, but its responsiveness to adrenaline low.[59]

Several studies showed that the low resting diastolic blood pressure of high fit/well-trained subjects is coupled to a reduction in peripheral vascular resistance.[275, 397, 398, 381] In chapter 5 the more fit subjects had larger vasodilatory responses to stress and in chapter 6 increased vasodilatory responding to stress was found after long-term training. These various findings are in agreement with adrenaline-infusion experiments, where well-trained subjects show enhanced vasodilation that was held to reflect increased β-2-receptor sensitivity of the vessels in endurance trained muscles. Since chronic stress has been associated with a desensitization of β-2-receptors in the two-stage model, it is feasible that fitness training counteracts the effects of stress on blood pressure by "protecting" β-receptors from down-regulation. Unfortunately, the findings of impaired β-receptor up-regulation during exercise have not been replicated, and extensive comparison of hypertensives with their age- and sex matched controls did not suggest any differences in adrenoceptor characteristics and reactivity.[212] In addition, the effects of fitness (training) on β-receptor functioning are still unclear. In endurance athletes, β-2-receptor density on blood cells and sensitivity has been found to be increased[335, 28, 361] as well as decreased[71, 430] , whereas physical training had no effects.[612] Jost et al.[280] showed that athletes had low β-receptor density during periods of endurance training, but high density during periods of sprint training, which may partly explain the inconsistent findings. More consistent effects were found at the muscular level. Red "aerobic" slow-twitch fibers have larger β-2-receptor density than white "anaerobic" fast-twitch fibers in animal and man, accounting for the larger oxidative capacity of the former.[167, 380] Furthermore, rat studies showed that β-2-receptor density in skeletal muscle is trainable, with the increase again limited to the slow-twitch fibers.[613] However, the increase in β-2-receptor density may be limited to the fibers themselves; β-2-receptor density of the *arterioles* of muscles composed of predominantly fast or slow twitch muscles was identical.[380] Only the number of arterioles was remarkably larger in slow twitch muscle. This suggests that the main difference explaining the stronger vasodilatory response to adrenaline in aerobically trained muscles is not due to adrenoceptor responsiveness but simply to the larger capillary beds.

These findings clearly argue against the suggestion that exercise prevents stress-induced hypertension by countering β-receptor down-regulation. However, most of the research cited depended on the use of white blood cells as a model for β-receptor functioning. Although the number of β-receptor binding sites on lymphocytes is related to the number of such sites on heart and lung tissue, it is unclear to what extent receptors on blood cells mirror adrenoceptors on other tissues (fat cell, vessels). It can also be doubted whether the in vitro binding studies have meaning for functional organ responses in vivo. Results may have been further confounded by stress/exercise induced changes in subpopulations of human lymphocytes. Therefore, the interesting idea that negative effects of stress as well as positive effects of exercise accumulate on receptor functioning deserves to be used as a working hypothesis in future research. Nonetheless, as far as the

blood pressure regulation is concerned, the most striking difference between chronic stress and regular exercise appears to be their opposite influence on the vascular resistance of skeletal muscle tissue. It is possible that regular exercise simply compensates the vasoconstriction characteristic of chronic stress and established hypertension by increased capillarization.

Cholesterol

So far I have concentrated on the cardiovascular system only. However, many of the metabolic determinants of cardiovascular disease may show opposite effects of stress and exercise. Cholesterol is the first example of these. Basal levels of total cholesterol, LDL-C and triglycerides are known to be lower in the high fit exercisers, whereas levels of the favorable HDL-C are higher (see chapter 2). Controlled training studies have shown that the beneficial shift in the lipid profile can be brought about by taking up exercise, and an example of this was found in chapter 7, where fitness training was seen to lower total cholesterol. Two key enzymes are thought to play a major role in the beneficial effects of training.[616] Lipoprotein lipase, which helps to convert VLDL-C to HDL-C, is increased after exercise, probably because it improves the muscle's ability to utilize FFA as a fuel for endurance work. Activity of LPL is greater in aerobic slow-twitch fibers, than in anaerobic fast-twitch fibers, which may account for the higher levels of HDL found in the aerobically fit, who have greater ratios of slow-twitch to fast-twitch fibers. A second enzyme, hepatic lipase, is believed to play a major role in the conversion of HDL_2-C to the less favorable HDL_3-C. Hepatic lipase activity decreases in response to exercise, and this is probably linked to the exercise-related change in body fat, which could explain the strong dependency of the lipid effects on weight loss seen in some training studies.[317]

While there is incomplete evidence that mild forms of episodic or chronic stress like student examination[177, 128, 428, 423] or work demands[296, 387, 537, 431] are associated with systematic alterations in lipids and lipoproteins, more severe forms of stress do appear to alter lipid levels. Two months after a severe earthquake (6.8 Richter) that left 280.000 people homeless, total cholesterol and triglyceride levels of the survivors were significantly elevated above those of an age- and weight matched control group.[578] Notification of selection for active military duty in a combat area was likewise associated with a rise in total cholesterol.[205] Studies linking low control over one's work environment (decision latitude) to higher cholesterol have been inconclusive[452] , but unemployment[296] , occupational instability[516] , and the direct threat to unemployment[386] significantly increased total cholesterol. Further evidence for psychosocial influences on lipid metabolism comes from studies linking high cholesterol levels to (subscales of) the type A behavior pattern[198, 358] , depression[127, 128] , and low social support.[571] Part of these psychosocial stress on cholesterol may be mediated through changes in diet and smoking, but a direct influence on lipid metabolism through a prolonged sympathetic nervous system activity cannot not be ruled out. There is a systematic increase in FFA levels during acute mental stress[117, 501, 331, 377] , that is due to the combined action of adrenaline and

noradrenaline. Noradrenaline stimulates β-1-receptors in adipose tissue, and may also affect lipoprotein lipase and hepatic triglyceride lipase activity, thereby increasing LDL-C and decreasing HDL_2-C.[246, 499, 272] At the same time, adrenaline stimulates the adipose tissue to release free fatty acids by its simultaneous effects on β-2-receptors controlling adipose tissue blood flow and on β-1 and β2-mediated adipose lipolysis.[362, 598, 346] When produced in excess, free fatty acids are transformed into triglycerides and secreted into the plasma as VLDL-C. These may form the basis of the acute increase in the level of total cholesterol and triglycerides during mental stress.[127, 15, 558, 105]

Nothing is presently known about the FFA response to stress in the trained compared to the untrained. However, since adrenaline responses are equal in these groups, one would expect greater FFA increases in the trained, based on their greater β-2-receptor sensitivity. Part of this greater lipolytic potential may be compensated by the selective loss of abdominal fat versus femoral and gluteal fat, since abdominal adipocytes are more responsive to catecholamine-induced lipolysis than are femoral adipocytes.[616] However, during adrenaline infusion, FFA level is significantly more increased in the trained state.[383] Consequently, we should expect greater increases in cholesterol during acute stress in the trained. Taken the otherwise clear advantage of training on the basal levels of cholesterol and triglycerides, lipolysis may represent an excellent example of how enhanced short-term reactivity of a system may be coupled to a favorable level of its risk factors for cardiovascular disease. Alternatively, short-term catecholamine and FFA reactivity by itself may not be crucial to stress-induced increases in cholesterol. Cortisol, apart from increasing FFA itself, stimulates cholesterol synthesis[81] , and FFA to cholesterol conversion.[581] Moreover, adrenocorticoids may lower HDL-C by depressing LPL-activity.[272] Therefore, stress may increase cholesterol predominantly when there is additional involvement of the pituitary-adrenocortical axis.

Aggregation, coagulation and fibrinolysis

Prospective studies on hemostatic factors have identified two important risk factors for cardiovascular disease: fibrinogen and PAI-1 activity. High fibrinogen was a potent predictor for cardiovascular death and stroke, independent of the classical risk factors.[393, 609, 294] Suggested pathogenic effects of fibrinogen include increases in viscosity, platelet activation, and platelet aggregation, factors that play an important role in atherogenesis. Even without its effect on atherosclerosis the importance of fibrinogen is not surprising. The conversion of fibrinogen to clots of fibrin threads is the final step in the formation of a thrombus, and various studies have shown that acute myocardial infarction is often precipitated by occluding intracoronary thrombosis (90% due to thrombi).[103, 579] Acute thrombosis represents a disturbance of the balance between fibrinolytic mechanisms that favor thrombus breakdown, and platelet, humoral, and vessel factors promoting thrombosis. Since the breakdown of thrombi is highly dependent on the activation of plasminogen by tissue plasminogen activator, increased activity of its inhibitor, PAI-1, may play a crucial role in intracoronary thrombosis. Indeed, high PAI-1 activity was found to be an independent predictor of myocardial reinfarction[215,

231] , and myocardial infarction patients are systematically distinguished from other patients (including angina pectoris) by high levels of PAI-1 activity.[415]

Although two studies have found improved fibrinolytic responsiveness after training[611, 169] , many others have failed to find such effects.[168, 138, 495, 258] Furthermore, various studies suggest that basal fibrinolytic activity may even be lower after training.[168, 611, 541] In combination with the unchanged activity of various coagulation factors,[169] this may suggest that training enhances, rather than reduces the risk for thrombosis. However, several studies show that the decrease in fibrinolytic activity is paired to a decrease in platelet aggregation in the well-trained, thereby restoring hemostatic balance.[124, 336, 525, 603] In addition, various other studies have suggested increased fibrinolytic potential after training through a reduction of PAI activity.[154, 541, 219, 559] In our own study (chapter 7), no clear cut training effects on PAI-1 activity were found, but it is possible that a training-induced reduction is found only in subjects who have high PAI-1 activity before training. Cross-sectional comparison of exercisers and non-exercisers did show lower levels of fibrinogen[541, 412] , and training was seen to actively reduce plasma fibrinogen by 13% in elderly[559] and by 17% in non-insulin-dependent diabetics.[258] In short, there is some evidence for improved hemostasis after training, but our knowledge is highly incomplete. It is fortunate that research in this direction is intensifying. Exercise training, in advantage over drug-related thrombolytic therapy, does not dramatically change the balance between coagulation and fibrinolysis like the former, with its inherent risk of bleeding. Moreover, exercise training could also be used preventively, unlike drugs.

At present, there is only indirect evidence for psychosocial influences on hemostasis. High fibrinogen levels were associated with higher job stress[376] and a social activity pattern indicative of low social support.[476] However, preliminary data show that both adrenaline infusion and mental stress directly affect the levels of platelet release products[340, 332] and factors controlling platelet aggregation, fibrinolysis, and coagulation.[333, 588, 276] The acute effect of both mental stress and adrenaline infusion is an increase in fibrinolysis. The increased fibrinolysis may be mediated by activation of t-PA through β-2-receptor stimulation, or by increased skeletal muscle blood flow (also β-2-related).[333] When stress is prolonged, it is possible that fibrinolysis starts to decrease through 1) a loss of β-2-receptor function, 2) increased levels of fibrinogen, 3) reduced muscle blood flow, or 4) a β-1 mediated reduction of the synthesis of prostacyclin, an important mediator of t-PA release.[569] This may result in a disequilibrium of the hemostatic balance in favor of coagulation, since adrenaline simultaneously activates platelet activation and coagulation. Note however, that much of the above effects have the status of a hypothesis only. One can only agree with Markowitz & Matthews, who called hemostasis and thrombosis "one potential area ripe for psychosocial investigation" (Markowitz & Matthews, 1991, p.643).[377]

Insulin-sensitivity

In the Paris Prospective Study, Fontbonne et al.[183] identified four independent predictors of CHD out of a broad set of potential risk indicators: the predictors were

systolic blood pressure, smoking, total cholesterol, and fasting plasma insulin level. Surprisingly, blood glucose, glucose tolerance, and non-insulin-dependent diabetes mellitus were not associated with an increased risk for cardiovascular disease. The high correlation between these latter variables and insulin levels may explain why previous prospective studies not accounting for insulin levels, have found these variables to be an independent predictor of CHD incidence and mortality.[291, 199] High plasma insulin levels may also be responsible for the atherogenic effects of abdominal obesity, another potent predictor of CHD incidence and mortality[330] , since insulin levels are highest in subjects with high central body fat.[183] High circulating levels of insulin have been hypothesized to promote atherogenesis by direct effects on the proliferation of smooth muscle and by promoting the flux of cholesterol into cells lining the arterial wall.[241] However, not all experimental evidence supports a direct causal link between insulin and atherogenesis.[479, 424] Therefore, hyperinsulinaemia may be atherogenic mainly by affecting other more plausible metabolic determinants of arterial damage, like HDL-C, triglycerides, LDL-C, platelet activity, coagulation factor VII, PAI-1 activity and blood pressure. The fact that this cluster of risk factors is a common clinical finding has given rise to the hypothesis that it is not constituted at random but is the multifaceted symptom of a basic abnormality, called "syndrome X", probably rooted in overweight and insulin resistance.[326, 469, 170, 283]

In cross-sectional comparisons, endurance-trained subjects have lower fasting insulin level, up to a 50% reduction in the insulin response to a carbohydrate challenge, and, despite the lower insulin concentrations, unchanged or slightly improved glucose tolerance.[595] A study using a hyperinsulinaemic, euglycemic clamp has further demonstrated increased insulin-sensitivity (i.e. enhanced glucose uptake) in muscle, liver and adipose tissue of endurance athletes[473] Short-term training programs were shown to increase insulin-sensitivity, to reduce the glucose-stimulated insulin response, and to lower resting plasma insulin levels in animals[563] , young and elderly human subjects[563, 306, 287] , cardiac patients[228] , obese subjects[106] , hypertriglyceridaemic subjects[325] , and insulin-dependent[327] and non-insulin dependent diabetics.[42, 319] The exact cause and the nature of the increased insulin-sensitivity are unclear. Enhanced insulin binding to its insulin receptor cell as well as post-receptor mechanisms have been invoked as explanations[595] , but these could be either primary or secondary to a blunted insulin secretion of the pancreatic β-cells seen in trained subjects.[303] The fact that insulin-sensitivity is not homogenous over different types of muscles may provide some clues. The aerobic slow-twitch fibers are known to have higher insulin sensitivity than the anaerobic fast-twitch fibers.[251] This could be related to the higher density of insulin receptors found in these fibers, or to the more profound capillarization. The latter explanation is favored by a study reporting a strong correlation between training-induced increases in muscle capillary density and the total glucose disposal rate during a hyperinsulinaemic, euglycemic glucose clamp.[345]

Does chronic stress affect insulin-sensitivity? If little was known about the fibrinolytic processes during emotional stress, even less is known about its effects on insulin metabolism, although stress has been known to aggravate the metabolic changes produced by diabetes and increase the insulin requirements.[155, 238] Several studies did

test the effects of adrenaline infusion (reviewed in MacDonald et al.).[362] The acute effects of adrenaline are an increase in blood glucose, partly through β-receptor mediated hepatic glucose output, partly by providing the muscles with FFA and intramuscular glycogen as alternative energy sources, and partly by impairing muscle glucose uptake. Initially, this hyperglycaemia is not followed by increased insulin levels, and some studies report adrenaline-mediated decrease in insulin. After 30-40 minutes of infusion however, plasma insulin begins to rise, indicating that the early suppression of insulin release is not maintained. This could well be indicative of a gradual decrease in insulin sensitivity when a stress-induced increase in plasma adrenaline is prolonged. Interestingly, adrenaline also impairs muscle glucose uptake during exercise, suggesting that exercise is as hazardous as stress. However, local hypoxia and muscle contraction counteract the catecholamine effects and give rise to a sharp increase in muscle glucose usage by non-insulin dependent glucose uptake and by directly increasing insulin-sensitivity.[595] The differential effects of exercise and emotional stress on insulin metabolism may provide us with one of the most clear examples of "uncoupling" of the adrenal-medullar nervous system activity and true muscle action.

Again, the action of the catecholamines may be less important then the action of the pituitary-adrenocortical axis. A highly interesting hypothesis was put forward by Brindley and Rolland.[56] They suggest that insulin resistance is precede by an increased control of metabolism by glucocorticoids during prolonged stress. Indeed, steroid hormones, particularly cortisol, are known to produce insulin resistance acutely and chronically, eventually followed by non-insulin dependent diabetes mellitus, as shown most dramatically in Cushing's syndrome.[470] Moderate elevations of plasma cortisol after cortisol administration was followed by marked insulin-resistance of both slow-twitch and fast-twitch muscle tissue in rats, but the effects were most pronounced in the aerobic slow-twitch fibers.[251] The body compensates for the glucocorticoid-induced insulin deficiency by increasing the circulating concentrations of insulin. Either the hyperinsulinaemia or insulin resistance itself in turn cause an increase in triglycerides, cholesterol and blood coagulability, which may lie at the basis of the increased risk for atherosclerosis after chronic cortisol load.[581]

If the strong links between hypertriglyceridaemia, hypercholesterolaemia, hyperinsulinaemia, hypofibrinolyis, hypercoagulability, and hypertension indeed have a common ground in insulin resistance, than the improvement of insulin-sensitivity may also explain many of the simultaneous beneficial effects of regular exercise described before. Chapter 7 provided preliminary evidence that such simultaneous training effects occur, but unfortunately no assessment of insulin, let alone insulin-sensitivity was made. However, the immediate importance of the exercise effects on insulin resistance for the syndrome X was clearly shown by the rat studies of Reaven.[469] Substituting fructose for the carbohydrate conventionally present in rat chow, rapidly led to insulin resistance with hyperinsulinaemia, hypertriglyceridaemia, and hypertension. All these effects were markedly attenuated when insulin resistance was prevented by exercise training. Therefore, if vasodilatory capacity was the potential candidate for a direct interactive effect of stress and exercise on the risk for hypertension, then insulin-sensivity seems the likely candidate for such an interaction on the risk for atherosclerosis. In fact the two

mechanisms may be directly related. Ferrannini & Natali suggest that the insulin-resistance of hypertensives may stem largely from an inability to shunt blood to target tissues, in particular to muscle and adipose tissue. This suggests that insulin-resistance is directly related to vasodilatory capacity. In a similar vein, enhanced muscle blood flow has recently been proposed as a main factor in peripheral HDL production[486] , and endothelial release of tissue plasminogen activator (the main fibrinolytic agent) may also be related to muscle blood flow.[149] Clearly, we have only just begun to understand the mechanism linking insulin-sensitivity to stress and CVD. However, if insulin metabolism does indeed play a crucial role, then a few hours of exercise a week might counter the detrimental effects of stress on blood pressure, cholesterol, insulin, and thrombosis simply by "preventive maintenance" of insulin-sensitivity.

Conclusions

In conclusion, long-term exposure to psychosocial stress and long-term exercise habits show completely opposite effects on most known or suspected pathogenic processes involved in cardiovascular disease. That fact alone should encourage the promotion of fitness programs to compensate the aversive effects of daily stress. The mechanisms leading exercise and stress to their opposite outcomes remain to be elucidated, and provide a great challenge for our future research. Much of the adverse effects of stress may be compensated by the increased vascularization of skeletal muscle after training. Furthermore, I suspect that receptor regulation (β-receptor, cortisol-receptor, insulin-receptor) will evolve as the site for a direct interaction between the effects of exercise and stress. In contrast to the highly dynamic, effort-oriented action of the autonomic nervous system that was the focus of our reactivity studies, receptor regulation represents a slower pathway that is more likely to be used in the adaptation to chronic stress. However, even if there is no interaction at all, and the effects of exercise and stress merely add up (albeit in opposite direction), then people who suffer from stress may still have greater benefit from exercise than others. Atherogenic factors like cholesterol, heart rate, blood pressure, and blood coagulability **synergistically** affect the integrity of the arterial walls, such that stress-induced increases in levels in any of these parameters serve to increase the pathogenic effect of all of the others. By virtue of that synergy alone, a reduction in the level in one or more of these parameters through training will be most effective if their joint levels are high, as is the case during chronic stress. Thus, there is good reason to believe that the protective effects of exercise are stronger in people suffering from stress.

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Summary

The main goal of this thesis was to show that fitness training counters the detrimental effects of stress on cardiovascular health. More specifically, fitness training was thought to improve psychological make-up, reduce the acute physiological response to stress, and counteract the effects of chronic stress on the cardiovascular risk factors.

In chapter 2, evidence is reviewed for a preventive effect of regular exercise on the development and progression of cardiovascular disease. It is noted that regular exercise is most effective when it causes an increase in aerobic fitness, and the relative risk for subjects in the least fit quartile is more than 4.8 times higher than that of subjects in the most fit quartile. Since smoking, blood pressure and cholesterol do not entirely explain the beneficial effects of regular exercise, it is hypothesized that exercising may partly protect against cardiovascular disease by preventing the detrimental effects of stress.

Chapter 3 elaborates on the possible role of physiological stress-reactivity in cardiovascular disease. Current psychosomatic theory regards the repeated and prolonged occurrence of autonomic nervous system activity (fight-flight reaction) as the main cause for stress-induced disease. During psychosocial stress-situations the sometimes fierce cardiovascular and metabolic responses are not "used up" by the muscles and this may result in increased blood pressure and atherosclerosis. Research has concentrated on the striking individual differences in the physiological stress-reactivity that occur during a variety of effortful mental stress tasks performed in the laboratory. Exaggerated reactivity to such stressors is thought to predispose the individual to cardiovascular disease.

Chapter 4 reviews 30 studies that have examined aerobic fitness as a possible mediator of the physiological stress-reactivity. Virtual all studies found that high fit subjects had lower heart rate and diastolic blood pressure levels during exposure to the stressors than low fit subjects. The lower stress levels were mainly based on lower basal levels in the high fit, but lower stress-reactivity was also seen to contribute in about half of the studies. In agreement with popular belief, this suggested that aerobic fitness training could be used to prevent the effects of stress on cardiovascular disease. However, some concerns remained. Most studies had been cross-sectional, comparing sedentary subjects with subjects who had been exercising for years. The favorable psychological and physiological profile found in regular exercisers (o.a. reflected in high aerobic fitness) does not necessarily follow from their exercise behavior. Alternatively, it depends on endowment and/or self-selection.

Chapters 5 and 6 present the results of two longitudinal studies that aimed to directly examine the effect of fitness training programs on psychological make-up and stress-reactivity. Aerobic fitness of these subjects was measured as the maximal oxygen consumption per kg body weight during an exhaustive exercise test (Vo_{2max}). Although all subjects were non-exercisers before the start of the study, substantial variation existed in their Vo_{2max}, probably reflecting hereditary influences. In the first study (N=26), these pre-existing differences in aerobic fitness were found to be related to cardiovascular reactivity during two stressful reaction time tasks. More fit subjects were found to have diminished vagal withdrawal during stress, and smaller diastolic blood pressure reactivity. However, these effects were not replicated in a second study (N=62), when the stress tasks were made far more challenging by team competition. In fact, more fit subjects showed higher systolic and diastolic blood pressure reactivity to the stressors. Both studies failed to show a relationship between fitness and important indices of sympathetic

nervous system reactivity like the pre-ejection period, cardiac output, or urinary catecholamine excretion. In chapter 5, seven weeks of training were not found to change either reactivity or recovery of any of the variables, although Vo_{2max} was seen to increase significantly. Chapter 6 replicated this lack of training effects in a larger group of subjects, using a training program of longer duration (4 to 8 months). In addition, no effect was found of fitness training on a host of psychological variables (e.g. neuroticism, anger expression, coping style, self-esteem and mood). The beneficial effects of training were limited to a reduction in the overall levels of heart rate and diastolic blood pressure.

Chapter 7 deals with the effects of exercise training on a cluster of CHD risk variables that may have a common background in insulin-insensitivity, i.e. body composition, cholesterol, triglycerides, and plasminogen activator inhibitor (PAI) activity, a risk indicator for disturbances in the coagulation/fibrinolysis balance. Total cholesterol and percentage body fat significantly decreased in response to training, and increased again during de-training. PAI activity always decreased in response to training, particularly in subjects with high initial PAI levels, but definite causality could not be established because of substantial seasonal shifts in the non-training control groups.

Chapters 8.1 and 8.2 of the general discussion summarize other recent studies on the effects of fitness training on psychological functioning and acute physiological stress-reactivity. It is hypothesized that the popular belief in stress-alleviating effects of exercise largely reflects its short-term neurophysiological effects on mood, blood pressure, and even reactivity. Lasting psychological benefits of exercise may be limited to subjects who experience severe psychological disturbances at the start of training. The psychological differences found between exercisers and non-exercisers in the population at large must predominantly reflect self-selection, i.e. emotionally well-adjusted, self-confident and self-disciplined persons may be most attracted to sports and exercise. None of the studies provided convincing evidence for an effect of training on stress-reactivity, even if initially low fit and high stress-reactive subjects were used. It is concluded therefore, that exercise does not increase the resistance to stress by influencing psychological make-up or acute psychophysiologic reactivity.

Chapter 8.3 re-evaluates the idea that a reduction in stress-reactivity is crucial to a beneficial effect of training. Reliability, intertask consistency, construct, predictive and ecological validity of cardiovascular reactivity to laboratory stress are reviewed, and it is concluded that reactivity may not be suited as a risk factor for cardiovascular disease. In fact, two-stage models of stress suggest that high sympathetic reactivity during acute exposure to stress may be a positive, rather than a negative trait, as long as it is paired to faster recovery and lower overall levels of heart rate, blood pressure, and metabolic risk factors during chronic stress.

Chapter 8.4 attempts to explore new ways to direct our future research on stress and exercise. It is noted that long-term exposure to psychosocial stress and long-term exercise habits show completely opposite effects on most known or suspected pathogenic processes involved in cardiovascular disease (coronary blood flow, triglycerides, LDL/HDL cholesterol ratio, plasma insulin, hypofibrinolysis, and hypercoagulability). Several possible sites for a direct interaction between chronic stress and regular exercise were explored, i.e. cardiac autonomic balance, adrenoceptor sensitivity, vascularization of skeletal muscle, and insulin-sensitivity. Although the exact mechanism remains to be found, it is concluded that fitness training should be seen as an excellent way to compensate or prevent stress-related deterioration of cardiovascular health, even if psychological make-up or the acute reactivity to stress are unchanged after training.

Samenvatting

Het is bekend dat een verhoging van de aerobe fitness door conditietraining een verlaging van het risico op hart- en vaatziekten geeft. Een afname van het cholesterolgehalte en de bloeddruk speelt daarbij een mogelijke rol, maar kan slechts een gedeelte van het preventieve effect van conditieverbetering verklaren (hoofdstuk 2). In dit proefschrift staat het effect van training op de lichamelijke reactie op stress centraal. In de laatste twee decennia is er een groeiende belangstelling voor individuele verschillen in de reactie op stress. Mensen met hevige lichamelijke reactie op stress worden geacht een groter risico te lopen op hart- en vaatziekten en er wordt naarstig gezocht naar mogelijkheden om de reactie op stress te verkleinen (hoofdstuk 3). Bij het zoeken naar verklaringen voor verschillen in stress-reactiviteit bleek dat sporters met een hoge aerobe fitness vaak een lagere hartslag en bloeddruk hadden tijdens stress dan niet-sporters met een lage aerobe fitness (hoofdstuk 4). Meestal dankten de fitte sporters hun lagere bloeddruk en hartslag aan een lagere rustwaarde, maar in de helft van de studies was ook de reactie op stress minder sterk. Het was echter niet duidelijk of de geringere stress-reactiviteit voortkwam uit het verschil in aerobe fitness tussen de groepen of uit een verschil in psychologische weerbaarheid tegen stress. Bovendien is onduidelijk in hoeverre sporters verschillen van niet-sporters als gevolg van het sporten zelf. Het is mogelijk dat bestaande verschillen in persoonlijkheid of aanleg voor aerobe fitness ertoe leiden dat sommigen wel gaan sporten en anderen niet.

In hoofdstuk 5 en 6 wordt een tweetal studies beschreven waarin de invloed van een trainingsprogramma op het psychologische profiel en de lichamelijke reacties op stress wordt gemeten bij ongetrainde personen. Voor aanvang van het trainingsprogramma bestonden er reeds aanzienlijk verschillen in aerobe fitness, die werd gemeten met een maximale inspanningstest. De bestaande verschillen in aerobe fitness, waarschijnlijk gebaseerd op een verschil in aanleg, bleken niet consistent met stress-reactiviteit samen te hangen. Wanneer er sprake was van sterke team-competitie bleek de bloeddrukreactie van de meer fitte personen zelfs heviger dan die van de minder fitte personen. Tevens bleek dat conditietraining geen effect had op het karakter van de deelnemers, noch op hun omgang met stress en emoties, hun stemming of hun lichamelijke stress-reactiviteit. De reacties op stress veranderden zelfs niet als een duidelijke verbetering van de conditie optrad of als de training van langere duur was (8 maanden). Alleen de absolute niveaus van hartslag en bloeddruk in rust, tijdens stress en direct na afloop van stress werden duidelijk lager als gevolg van training. Dit bleek gepaard te gaan met een afname van het totale cholesterolgehalte, het vetpercentage en mogelijk een verlaging van PAI activiteit, een risicofactor voor trombose (hoofdstuk 7).

De slotdiscussie (hoofdstuk 8) werpt een andere blik op de mogelijke effecten van conditietraining op stress dan die waarmee de trainingstudies werd aangevangen. Een trainingseffect op de psychologische weerbaarheid tegen stress wordt waarschijnlijk alleen gevonden bij mensen die veel last hebben van stress voor aanvang van de training. Over het algemeen zijn de bestaande psychologische verschillen tussen sporters en niet-sporters een gevolg van zelfselectie: emotioneel stabiele mensen met voldoende zelfdiscipline zullen eerder gaan sporten dan anderen. Een overzicht van alle recente trainingstudies toont duidelijk aan dat er geen trainingseffect te verwachten is op acute lichamelijke stress-reacties. Dit geldt voor mannen en vrouwen, voor jongeren en

ouderen en zelfs voor personen met een slechte beginconditie of een hoge stress-reactiviteit. Dit zou een teleurstellende bevinding zijn, ware het niet dat tegelijkertijd twijfel is gerezen over de voorspellende waarde van de in het laboratorium gemeten stress-reactiviteit voor het krijgen van hart- en vaatziekten. Het is mogelijk dat een hevige reactie op stress helemaal geen negatieve eigenschap is, zolang de acute reactie maar gekoppeld is aan een snel herstel en zolang het absolute niveau van hartslag en bloeddruk maar niet te hoog wordt. In dat geval zijn getrainde personen duidelijk in het voordeel omdat de gemiddelde niveaus van hartslag en bloeddruk tijdens stress duidelijk lager zijn dan bij ongetrainden. Mogelijk werkt conditietraining direct de effecten van chronische stress op belangrijke lichamelijke regelsystemen tegen, bijvoorbeeld door verandering van de autonome sturing van het hart, spiercapillarisatie of de gevoeligheid van hormoonreceptoren voor cortisol, adrenaline of insuline. In elk geval blijkt uit de literatuur dat regelmatige lichaamsbeweging en langdurige blootstelling aan stress een tegenovergesteld effect hebben op belangrijke risicofactoren als het triglyceride-, cholesterol-, en insulinegehalte en de bloedstolling.

De conclusie van dit proefschrift luidt dan ook dat training kan worden aanbevolen als een remedie tegen stress, ook al heeft ze geen invloed op de psychologische weerbaarheid tegen stress of de acute lichamelijke reactie op stress. Vrijwel alle ongunstige invloeden van chronische stress op de risicofactoren voor hart- en vaatziekten kunnen door conditietraining worden tegengegaan.

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