[Original article]

The CAREGENE study: genetic variants of the endothelium and aerobic power in patients with coronary artery disease

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Objectives Aerobic phenotypes show a wide variability to similar aerobic training stimuli, which can be partly attributed to heritability. Endothelial function affects aerobic power. Various physiological pathways may influence the endothelial function. Therefore, we aimed to examine whether polymorphisms of the eNos gene, the CAT gene, the VEGF gene, the GPX1gene, the subunit P22 phox of the NAD(P)H-odixase gene, the PPAR-*a* gene, and the PGC-*a* gene are associated with aerobic power or with its response to physical training in patients with coronary artery disease (CAD).

Methods 935 biologically unrelated Caucasian patients with CAD who had exercised until exhaustion during graded bicycle testing at baseline and after completion of 3 months of training were included in the CAREGENE study (Cardiac Rehabilitation and GENetics of exercise performance). Polymorphisms were detected using the invader assay and MassARRAY technology. Haplotype analysis was performed on the polymorphisms of the eNos gene, the VEGF gene and the NAD(P)H-oxidase gene.

Results Physical training significantly increased aerobic power by 24.2 ± 0.6% ($P < 0.001$). Associations of $P < 0.05$ were found between aerobic power and the eNOS 273C>T variant and the catalase -262C>T variant and aerobic power response. Haplotypes of the eNOS polymorhisms were predictive of aerobic power and its response to training ($P < 0.05$). After Bonferroni correction of multiple testing no significant differences remained.

Conclusion We believe that genetic factors are very important in the explanation of the great variability of aerobic power and its response. However, after Bonferroni-correction, differences in these polymorphisms remained no longer statistically significant.

Keywords *Coronary disease – endothelium – exercise – cardiac rehabilitation – polymorphism – oxygen uptake.*

INTRODUCTION

Coronary artery disease (CAD) is a major cause of death in Europe[1]. Lower aerobic power in CAD, expressed as peak oxygen uptake (peakVO_2), is independently associated with reduced survival rates[2]. It is well-established that physical activity improves survival[3], prevents the progression of CAD[4], improves endothelial function and increases aerobic power. Moreover, larger improvements in aerobic power with physical training are associated with greater reductions in cardiovascular risk factors[5] and mortality risk[6]. There is, however, considerable individual variation in aerobic power as well as in the response to physical training (virtually no gain to over 100%)[7], of which, particularly in CAD, the larger part remains unexplained[7]. Therefore, improved understanding of the determinants of aerobic power and of the response to training in CAD would be of substantial clinical relevance.

In cardiac patients age, sex, initial exercise performance, training dosage and smoking habits have previously been shown to account for 21% of the variation in aerobic power response to training[7]. Strong evidence also supports a considerable genetic contribution to aerobic power and the responses to physical training,

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i.e. the impact of genetic variation on aerobic power and its response to training has been reported to amount up to 66% [8] and 47% [9], respectively.

Nitric oxide (NO), released from the vascular endothelium in response to shear stress by increased blood flow during exercise[10], causes coronary and arterial vasodilatation, which in turn increases oxygen delivery to active tissues to support aerobic energy production[11].

NO-bioactivity is the result of (i) production of NO by the eNos (endothelial nitric oxide synthase); (ii) the inactivation of NO by subunit P22 phox of the NAD(P)H (nicotinamide adenine dinucleotide phosphate)-oxidase; (iii) the level of anti-oxidant genes such as gluthatione peroxidase (GPX), catalase (CAT), extracellular superoxide dismutase (ecSOD); (iv) other genes which have an indirect influence on the bio-activity such as vascular endothelial growth factor (VEGF) and peroxisome proliferator-activated receptor α (PPAR-α) and the peroxisome proliferator activated receptor gamma coactivator-1alpha (PGC-1α) [12]. It is therefore plausible that variation in one or more genes, encoding enzymes involved in endothelial function and NO-availability, may be associated with aerobic power or with its response to training.

In this part of the CAREGENE (CArdiac REhabilitation and GENetics of Exercise performance) study, we aimed to investigate whether polymorphisms of these endothelial related genes or their haplotypes [the polymorphisms of eNOS gene (-1495T>A, -949A>G, -813T>C, -786T>C, 273C>T, 298G>A), the CAT gene (-262C>T), the VEGF gene (405 and -460), the ecSOD gene (213A>G), GPX1 gene (197P>L), the P22 phox gene (640A>G and 242C>T), the PGC-1alpha gene (482G>S) and the PPAR-α gene (intron 7 C/G)] contribute to the individual variance in aerobic power or in the response to physical training in patients with CAD.

METHODS

The CAREGENE study design, inclusion criteria and protocol have been described previously[13]. Nine hundred and thirty-five biologically unrelated Caucasian CAD patients who had achieved evident exhaustion[14] during graded cycle exercise testing for determination of aerobic power at baseline and after three months of exercise training, were considered eligible for the CAREGENE study. The study protocol was approved by the Ethical Committee of the Faculty of Medicine of the Catholic University of Leuven and written informed consent was obtained from each participant.

Patients completed a three-month ambulatory supervised exercise training programme (90 minutes/session and involving cycling, running, arm crank, rowing, predominantly isotonic callisthenics and relaxation). Exercise intensity was individually determined by heart rate and progressively increased for each patient separately. Training frequency averaged 2.27 ± 0.02 times/week and training intensity was $79.7 \pm 0.35\%$. The latter was calculated as: (training heart rate/peak heart rate) $\times$ 100, where the mean training heart rate of the last three exercise sessions and peak heart rate at the end of the three-month training period were used.

Before and after the three-month training programme patients completed a maximal graded exercise test on a bicycle ergometer with respiratory gas analysis. The initial workload of 20 W was increased until exhaustion by 30 W every 3 minutes until 2000 and by 20 W every min thereafter. Heart rate was measured throughout the test with a 12-lead ECG (Max Personal Exercise Testing®, Marquette, Wisconsin, USA) and blood pressure was measured every 2 minutes (STBP-780® device, Colin, Komaki, Japan). Respiratory data were measured through breath-by-breath device using a 2900Z® (Sensormedics, Bilthoven, The Netherlands) until 1994 or an Oxycon Alpha® (Jaeger, Mijnhardt, Bunnik, The Netherlands) after that date. A detailed description of the exercise test methodology has been reported previously[13].

DNA was extracted from white blood cells using the 'salting-out' method. The invader TM assay (Third Wave Technologies) was used. The Invader assay combines structure-specific cleavage enzymes and a universal fluorescent resonance energy transfer (FRET) system. When the gene-specific probes bind the target, these enzymes will cleave. This mechanism warrants the specificity for distinguishing between alleles, whereas the FRET system generates an amplified read-out[15]. In every experiment synthetic target oligonucleotides were used as controls. Third Wave Technologies designed and provided all reaction components. Genotyping was performed in a 96-well format. By combining Probe mix (211 μl), Cleavase enzyme (79 μl) FRET mix (317 μl) and MAP buffer (26 μl) the reaction mixture was prepared. Of this mixture 6 microlitres were added into a 96-well plate. Six microlitres of no target blank, synthetic target oligonucleotides, or genomic DNA samples (50 ng/μl) were added. After short centrifugation and incubation at 63°C for 4 hours, fluorescent intensities were measured using a fluorescence microtitre plate reader. By calculating the ratios of the net wild type and net mutant signals[16], genotypes were determined. The analysis was repeated once on those samples where no genotype could be obtained during initial testing. Samples were excluded from the analysis when genotyping failed twice. In practice, this failure rate varies between 1.4% and 5.1% (data not shown). It seems that either impurities in or the quality of the DNA-samples interferes with the Invader reaction to a larger extent than they would

Table 1 Clinical characteristics for biologically unrelated Caucasian CAD patients (n = 935) in the CAREGENE study

Variable (number)	Overall cohort (935)
Women	76 (8)
Age (years)	56 ± 0.3
Body mass index (kg.m-2)	25.8 ± 0.1
Patients with history of	
diabetes	49 (5)
hypertension	251 (27)
Smoking habits	
current smoking	45 (5)
past smoking	681 (73)
Complaints in everyday living	
angina	41 (4)
dyspnoea	149 (16)
Reasons of referral	
AMI	630 (67)
anterior	252 (27)
inferior	333 (36)
CABG	377 (40)
PCI	470 (50)
Angina	23 (2)
Drug therapy	
Beta blockers	794 (85)
Antiplatelets	829 (89)
ACE-inhibitors	222 (24)
Hypolipaemic drugs	167 (18)
Calcium antagonists	84 (9)
Molsidomine	68 (7)
Nitrates	42 (5)
Digitalis	65 (7)
Diuretics	43 (5)

AMI: acute myocardial infarction, CK-MB: creatine kinase, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention. Some patients had more than one pathology. Data are presented as means ± SE for continuous variables and as numbers (percentage) for dichotomous variables. None of the patient characteristics at baseline were significantly different among genotypes of the genes.

do in PCR approaches, at least in our hands. Genotypes in the Ec-sod gene were determined by Lark technologies (Essex, UK) using the Sequenom MassARRAY technology. This technique is based on single-base primer extension and a detection based on matrix-assisted laser desorption ionisation time-of-flight (MALDI-TOF).

Data were analysed using SAS statistical software version 9.1 for Windows (SAS Institute Inc, Cary, NC, USA). Data are reported as means ± SE or as number of patients with percentage for dichotomous variables. To test whether the observed genotype frequencies were in Hardy-Weinberg equilibrium a χ^2-test with one degree of freedom was used. Distributions were checked for normality with the Shapiro-Wilk statistics. Comparisons between the exercise test at baseline and after training were made by paired student's *t*-test. To test potential relationships between gene variation and aerobic power or the response to training, a model, that tested the genotype effect, was used. This model includes analysis of the raw and of the adjusted data by ANOVA and ANCOVA, respectively. Where significant, the latter was followed by Fisher's protected LSD.

Where appropriate, categorical data were tested by χ^2 or by Fisher's exact test.

Haplotypes were constructed using the Phase® (version 2.1) [17]. Al statistical tests were two-sided at a significance level of 5%.

RESULTS

A selection of relevant clinical characteristics of the overall CAREGENE study cohort (n = 935) is listed in table 1. Aerobic power at baseline averaged 1716 ± 16 ml × min^{-1} or 77.9 ± 0.6% of predicted healthy values and ranged between 537 and 3326 ml × min^{-1}. Aerobic power increased with physical training by 24.2 ± 0.6% ($P < 0.001$), ranging from a decrease of 33.6% to an increase of 111.1%. Training dosage was comparable across the genotypes and haplotypes. At peak exercise, respiratory gas exchange ratio was 1.14 ± 0.003 at baseline

Table 2 Genotype-frequencies of 15 polymorphisms of the endothelial-related genes in biologically unrelated Caucasian CAD patients in the CAREGENE study

Genotype	Wild type	Heterozygous mutation	Homozygous mutation
eNOS -1495T>A	34.7	46.6	18.7
eNOS -949A>G	33.4	48.4	18.2
eNOS -813T>C	24.7	59.0	16.3
eNOS -786T>C	35.7	46.3	18.0
eNOS 273C>T	35.0	53.0	12.0
eNOS 298G>A	38.7	47.6	13.7
CAT -262C>T	60.3	34.1	5.6
VEGF -460	24.0	50	26.0
VEGF +405	44.0	11.0	45.0
ecSOD 213A>G	97.1	2.9	0
GPX 197P>L	50.7	49.2	0.1
p22 phox 640A>G	25.6	47.8	26.7
p22 phox 242C>T	44.4	45.4	10.2
PGC1α 482G>S	43.9	42.7	13.4
PPARα intron 7 G\C	64.8	30.2	5.0

Data are presented as percentages.

Table 3 Baseline aerobic power and the response to physical training, according to genotypes of the different genes

Gene		Genotype	VO_2pre (ml)*	F-(*P*)-value	ΔVO_2 (%)#	
ENos	T-1495A	TT (n = 313)	1736 ± 21	2.01 (0.13)	24.7 ± 0.9	0. 60 (0.54)
		TA (n = 420)	1697 ± 18		23.5 ± 0.8	
		AA (n = 169)	1761 ± 29		24.4 ± 1.3	
	A-949G	AA (n = 298)	1739 ± 22	1.38 (0.25)	24.5 ± 0.9	0.76 (0.46)
		AG (n = 432)	1706 ± 18		23.2 ± 0.9	
		GG (n = 162)	1759 ± 30		24.4 ± 1.3	
	T-813C	TT (n = 227)	1728 ± 25	0.36 (0.70)	25.2 ± 1.1	0.69 (0.50)
		TC (n = 542)	1711 ± 16		23.7 ± 0.7	
		CC (n = 150)	1737 ± 31		24.6 ± 1.3	
	T-786C	TT (n = 315)	1715 ± 21	0.53 (0.59)	25.1 ± 0.9	0.69 (0.50)
		CT (n = 408)	1706 ± 19		23.7 ± 0.8	
		CC (n = 159)	1742 ± 30		24.5 ± 1.3	
	C273T	CC (n = 310)	1736 ± 21	1.87 (0.15)	24.5 ± 0.9	1.88 (0.15)
		CT (n = 470)	1700 ± 17		24.6 ± 0.7	
		TT (n = 107)	1769 ± 36		21.3 ± 1.6	
	G298A	GG (n = 344)	1752 ± 20	4.36 (0.01)	25.1 ± 0.9	1.04 (0.35)
		GA (n = 424)	1685 ± 18		23.9 ± 0.8	
		AA (n = 122)	1775 ± 34		22.7 ± 1.5	
Catalase	T-262C	TT (n = 521)	1735 ± 16	0.72 (0.49)	22.9 ± 0.7	3.6 (0.02)
		TC (n = 296)	1702 ± 22		26.0 ± 0.9	
		CC (n = 48)	1723 ± 53		25.1 ± 2.3	
VEGF	405	GG (n = 404)	1735 ± 19	0.84 (0.43)	24.0 ± 0.8	0.64 (0.52)
		GC (n = 100)	1703 ± 18		24.2 ± 0.8	
		CC (n = 422)	1731 ± 37		24.9 ± 1.6	
	460	CC (n = 224)	1727 ± 25	0.19 (0.83)	23.1 ± 1.1	0.64 (0.52)
		CT (n = 462)	1724 ± 17		24.3 ± 0.8	
		TT (n = 244)	1708 ± 24		24.7 ± 1.0	
Ec-SOD	C760G	CC (n = 876)	1718 ± 13	1.75 (0.19)	23.7 ± 0.6	2.40 (0.12)
		G-carrier (n = 26)	1815 ± 72		28.7 ± 3.2	
GPX	Pro197Leu	Pro197Pro	1719 ± 18	0.00 (0.98)	25.0 ± 0.8	1.77(0.18)
		Leu-carrier	1719 ± 18		23.5 ± 0.8	
P22Phox	A24G	AA (n = 228)	1724 ± 25	1.39 (0.25)	24.0 ± 1.1	0.25 (0.78)
		AG (n = 426)	1738 ± 18		24.5 ± 0.8	
		GG (n = 238)	1688 ± 24		23.5 ± 1.1	
	C242T	CC (n = 413)	1735 ± 16	0.31 (0.73)	24.2 ± 0.8	0.06 (0.94)
		CT (n = 422)	1702 ± 22		23.9 ± 0.8	
		TT (n = 95)	1730 ± 38		24.5 ± 1.7	
PparaGC1A	Gly482Ser	GG (n = 377)	1712 ± 19	0.53 (0.59)	24.0 ± 0.8	0.23 (0.80)
		GS (n = 391)	1705 ± 19		24.7 ± 0.8	
		SS (n = 113)	1746 ± 35		23.9 ± 1.5	
Ppara	Intron 7G/C	GG (n = 566)	1716 ± 16	0.14 (0.87)	24.6 ± 0.7	0.67 (0.51)
		CG (n = 270)	1711 ± 23		24.1 ± 1.0	
		CC (n = 39)	1745 ± 61		21.6 ± 2.6	

*Adjusted for age, sex, height, weight. #adjusted for age, sex, height, weight and aerobic power baseline(ΔVO_2). Values are means ± SE. Analysis of (co)variance was used to compare means. F-value and level of significance (*P* value) of the an(c)ova are presented.

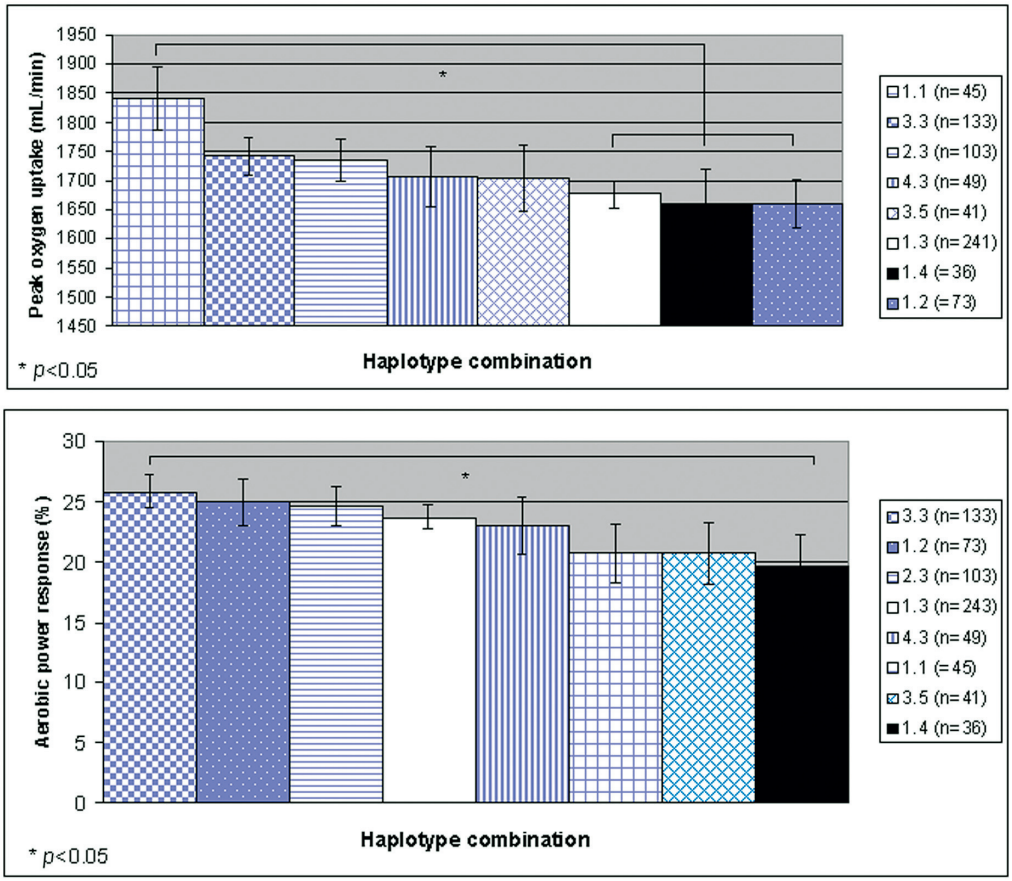

Fig. 1 Aerobic power and aerobic power response according to haplotype combinations. Covariate-adjusted (age, sex, height, weight) aerobic power (ml × min^{-1}) at baseline (a) and covariate-adjusted (age, sex, height, weight and aerobic power at baseline) aerobic power response (b) according to haplotype combinations of 6 common eNOS gene polymorphisms T-1495A, A-949G, T-813C, T-786C, C273T and G298A in biologically unrelated Caucasian CAD patients in the CAREGENE study. 26 haplotypes were observed in these patients. 5 haplotypes were renamed from numbers 1 to 5: AGTCTA (1), AGTCCG (2), TACTCG (3), TACTTA (4) and TATTCG (5). #$P < 0.05$ between 1.1 and 1.2, 1.3 and 1.4 for aerobic power. *$P < 0.05$ between 3.3 and 1.4 for aerobic power response.

and 1.13 ± 0.002 after training; peak ventilatory equivalent for oxygen was 38 ± 0.2 and 37 ± 0.2, respectively.

Genotype frequencies of the studied polymorphisms are shown in table 2.

Except for the genotype distribution for -813C>T and 273C>T of the eNos gene and the Pro197Leu polymorphism of the GPX gene all genotype distributions were in agreement with the prediction by the Hardy-Weinberg equilibrium ($P > 0.05$, χ^2-test, df = 1).

Table 3 shows aerobic power at baseline and the response to training according to genotypes of the investigated genes. Patients heterozygous for the 298G>A polymorphism of the eNOS-gene had a higher aerobic power at baseline than the homozygotes ($P = 0.01$). The homozygous wild-type carriers of T>C262 polymorphism of the catalase gene were associated with a lower aerobic power response to physical training compared with the C-allele carriers ($P = 0.02$). For the other genes no significant associations were found between genotype and aerobic power or aerobic power response to physical training ($P > 0.05$).

Haplotypes were constructed for the eNOS gene, the VEGF-gene and P22 phox gene.

With eNOS-polymorphisms -1495T>A, -949A>G, -813T>C, -786T>C, 273C>T, 298G>A we observed 26 haplotypes in these patients. Five haplotypes accounted for 90% of all haplotypes, and were renamed from numbers 1 to 5: AGTCTA (1), AGTCCG (2), TACTCG (3), TACTTA (4) and TATTCG (5), and subsequently included in the analysis. Haplotype frequencies were 26%, 13%, 42%, 6% and 3%, respectively. Only 8 of 15 possible combinations (n > 30) were observed accounting for 77% (n = 721) of all CAD patients in this study. At baseline the 1.1 homozygous haplotype (1842 ± 54 ml min^{-1}) was associated with a higher aerobic power than the 1.2, 1.3 and 1.4 haplotype combinations (1660 ± 43 ml min^{-1}, 1676 ± 23 ml min^{-1} and 1660 ± 61 ml min^{-1}, $P < 0.05$). The aerobic training response was also lower

in the patients with the 1.4 haplotype combination (19.5 ± 2.7 %) than the 3.3 haplotype combinations (25.9 ± 1.4%, $P < 0.05$).

Aerobic power and its response were not significantly different for the haplotype combinations of the VEGF gene or the P22 phox gene.

DISCUSSION

To our knowledge, the present study is the first to evaluate a potential association between aerobic power, its response to physical training and endothelium-related genes. Our results show that: (1) patients heterozygous for the 298G>A polymorphism of the eNos-gene had a higher aerobic power at baseline than the homozygous; (2) the homozygous wild-type carriers of T>C262 polymorphism of the catalase gene were associated with a lower aerobic power response to physical training compared with the C-allele carriers; (3) between the haplotypes of the ENos-gene polymorphisms we found differences for baseline aerobic power and response to training. However, the significant results disappear after correction for multiple testing.

The delivery of oxygen to muscles during exercise is of critical importance to attain high levels of aerobic power. Vascular endothelial-derived nitric oxide (NO) plays an important role in coronary and peripheral artery vasodilatation, vascular tone and blood pressure regulation. NO release from the vascular endothelium dilates blood vessels in response to the blood flow increase with exercise, thereby enhancing substrate and oxygen delivery to the working muscles.

Endothelial NO bioactivity is the result of (i) production of NO by the ENos-gene; (ii) the inactivation of NO by P22 phox-gene; (iii) the level of anti-oxidant genes such as gluthatione peroxidase (GPX), catalase, extracellular superoxide dismutase (ecSOD); (iv) other genes which have an indirect influence on the bio-activity such as vascular endothelial growth factor (VEGF) and PPARα-genes[18].

In patients with CAD, chronic exercise has been shown to result in increased vascular NO levels by upregulation of eNOS gene expression in endothelial cells, i.e. 4 weeks of training increased eNOS protein expression by 2-fold and eNOS phosphorylation levels by 4-fold in the left internal mammary artery endothelium[19].

The eNOS gene is probably one gene in which genetic variation may contribute to the individual variation in aerobic power or its response to physical training. Forearm blood flow (in interaction with physical fitness level) in healthy Caucasian women[20] and correction of endothelial dysfunction after physical training in CAD patients[21] have previously been reported to be dependent of the eNOS genotype. However, the association between genetic variation in the eNos gene and aerobic power or the response to physical training has not been investigated yet.

In a previous study in patients with CAD, one promoter polymorphism (–786T>C), was associated with training-induced improvement in endothelial function[21]. In that study, unfortunately, the aerobic power response to training was not measured. Gly298Asp was not associated with the correction of endothelial dysfunction after physical training. Although the Glu298Asp polymorphism affects endogenous NO production, an effect on NO-mediated vascular responses was also not observed either in healthy volunteers[22] or in patients with CAD[23]. Our better results for patients with the Asp298Asp for aerobic power at baseline were not in agreement with the lower NO-release described in many studies.

Conversely, in chronic heart failure patients physical training did not increase eNos expression. They observed an increased expression of the antioxidative enzyme genes which reduced oxidative stress and hence may account for an increase in vascular NO mediated vasodilation[24].

CAT is an anti-oxidant enzyme that catalyses the decompensation of hydrogen peroxide to oxygen and H_2O and has influence on the NO availability[25]. A study of Forsberg found that catalase levels were significantly higher in donors carrying the T-allele in comparison to donors for the c-allele[26]. A higher level of this anti-oxidant gene has an influence on the NO-release. A study of Christiansen indicated a modest association between CAT–262TT homozygosity and improved physical performance as assessed by grip strength[27]. No studies about the catalase polymorphisms and aerobic power and response to training have been published.

The GPX, ecSOD, P22 phox, have also an anti-oxidative effect. In our study no significant differences for baseline aerobic power and its response to training were observed for polymorphisms of these genes.

Finally, the PPAR*α*-genes and the VEGF gene were reported in our study.

Peroxisome proliferator-activated receptors (PPAR) have a great influence on the fat acid oxidation in the muscles. Activators of PPAR*α* (lipid-lowering fibrate derivatives) and PPAR*γ* (antidiabetic thiazolidinediones) reduce the expression of p22 phox and p47 phox, decrease NAD(P)H oxidase activity and ROS production, and increase CuZnSOD and catalase expression and NO release in endothelial cells[18]. PPARα-genes were associated with physical performance and myocardial infarction[28].

The vascular endothelial growth factor (VEGF) is a major angiogenic factor and is a prime regulator of

endothelial cell proliferation. For the migration and proliferation of endothelial cells VEGF needed NADH-oxidase derived ROS. Studies reported that polymorphism of the VEGF-gene has an influence on the severity of CAD possibly because of reduced VEGF expression[29]. Heart failure patients following exercise training have an increased expression of VEGF[30].

The indirect effect of these genes on the NO-release had no influence on the aerobic power and its response to training in our study. No other studies have been published about this population.

Metzger et al. studied three important polymorphisms of the eNOS gene and their association to the NO-formation. They concluded that eNOS gene variants combined within a specific haplotype modulate NO formation, although individual eNOS polymorphisms probably do not have major effects[31]. Concordant with these results we show here that, although one of the six polymorphisms of the eNOS gene shows differences for aerobic power only, better results were found for aerobic power and response to physical training when we looked at the haplotype combinations.

Our study has some limitations. First of all, the lack of objective measurements of endothelial function and values of NO-availability which could support our hypothesis of a link between NO-formation in all of the studied polymorphisms, should be noted. This could, however, be an area of future research. Further we used $P < 0.05$ to detect significant associations. We proved that there are some associations between the polymorphisms and aerobic power and its response to physical training. However, if we apply the Bonferroni comparison of means to take the 15 polymorphisms into account, a $P < 0.003$ should be used. Furthermore, studies in subjects of similar ethnicity, like the CAREGENE study, are more likely to detect gene effects that are specific to that particular ethnic subgroup. Therefore our findings should not be generalized to a broader and more diverse population which warrants more extensive research.

CONCLUSION

We believe that genetic factors are very important in the explanation of the great variability of aerobic power and its response but no significant differences were found in these polymorphisms. A better understanding of the genetic determinants of aerobic power and of the response to training in CAD patients would add substantial clinical relevance allowing optimization of the training programmes.

CONFLICT OF INTEREST: none declared.

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