
Running head: ACE gene and aerobic power in CAD

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Introduction

In coronary artery disease (CAD) the individual variation in aerobic power and the response to physical training are largely unexplained.[1]

The gene coding for the angiotensin-converting enzyme (ACE) is expressed in several types of somatic cells, including vascular cells, heart, lung and muscles.[2] Intronic 16 contains a polymorphism characterized by the presence (insertion, I) or absence (deletion, D) of a 287bp Alu repeat sequence [3], which has been associated with endurance-related phenotypes and the response to training [4].

The aim of the present study was to investigate the role of ACE I/D polymorphism on aerobic power and its response to physical training in patients with CAD included in the CAREGENE (CAdiac REhabilitation and GENetics of Exercise performance) Study.

Patients and methods

PATIENTS
Biologically unrelated Caucasian patients with CAD [56 (0.3) years] (mean (SE)) who had achieved evident exhaustion during graded cycle ergometer testing before and after 3 months of physical training (3 sessions weekly) from 1990 through 2001 (n=1095), were eligible for inclusion. The methods for graded exercise testing and training have been described in detail previously.[1] In 933 patients (m/f: 857/76) the ACE I/D polymorphism was analyzed. Patients were referred after myocardial infarction (68%), CABG (40%) and PTCA (50%).

ACE I/D GENOTYPE DETERMINATIONS
Polymerase Chain Reaction (PCR) of the specific gene sequence was performed as described.[3] PCR products were subjected to electrophoresis in an ethidium-bromide stained 1% agarose gel. Genotypes were confirmed using the sequenom MassARRAY Technology (Lark technologies, Essex, UK).

STATISTICAL METHODS
A χ²-test was used to test categorical data and Hardy-Weinberg equilibrium. Comparison at baseline v after training was performed by paired Student’s t test; comparisons of adjusted means across the ACE II, ID and DD genotypes by ANCOVA. Covariates had been identified a priori by stepwise regression.[1] Where required, ANCOVA was followed by Fisher’s protected least significant difference. Given allelic co-dominance is often missing [2], the allelic effect was also tested by comparing II-patients v D-allele carriers. Analyses were performed on the whole group as well as in 2 subgroups of 1) patients receiving ACE-inhibitor therapy (n=193) and 2) patients who were not on ACE-inhibition (n=688). Statistical tests were 2-sided at a significance level of 5%.
Results

ACE-GENOTYPE
In men v women frequencies of the I- and D-allele (0.47 v 0.41 and 0.53 v 0.59, respectively) and of the II, ID and DD genotype (0.23 v 0.18, 0.47 v 0.46 and 0.30 v 0.36, respectively) were similar, thus data for men and women were pooled. Hardy Weinberg equilibrium was maintained. Age, sex, body mass index, history of diabetes or hypertension, smoking habits, ejection fraction, cardiac pathology, interventions, drug intake and training dosage were comparable between subgroups and across ACE genotypes.

AEROBIC POWER AND RESPONSE TO TRAINING
Aerobic power at baseline was not significantly determined by ACE I/D genotype (Table 1). Covariate-adjusted aerobic power response to training was larger in ACE II v ID patients and v D-allele carriers in the whole group and in patients who were not on ACE-inhibition.

Discussion
The present study in 933 patients with CAD included in the CAREGENE study describes an independent association of the ACE I/D polymorphism with the aerobic power response to physical training in favor of the II genotype.

Although the physiological pathway is unclear, involvement of the renin-angiotensin system is conceivable. Higher tissue ACE mRNA expression, elevated levels of circulating ACE and increased bradykinin degradation are described in D-allele carriers. This may impair endothelium-dependent vasodilatation and aerobic pathways.

The effect is, although significant, rather small and may not be biological. If biological, the responsible locus may be located within the ACE-gene or in 1 to several nearby genes linked to the I/D polymorphism. Given the maintained Hardy-Weinberg equilibrium and genotype distribution in keeping with other studies, survivor bias is unlikely to have affected the study outcome.

A homogenous cohort of Caucasian patients with CAD was used; our findings should thus not be generalized. It is noteworthy that most patients (85%) were on beta-blocker treatment. Reactive renin stimulation after ACE-inhibition is prevented by concomitant beta-blockade, which markedly reduces plasma renin levels in these patients. [5]
Table 1. Peak oxygen uptake (mL · min⁻¹) at baseline and after physical training and the percentage response according to ACE I/D genotypes for 933 biologically unrelated Caucasian CAD patients and for the subgroup not taking ACE-inhibitors in the CAREGENE Study

<table>
<thead>
<tr>
<th>Patients</th>
<th>Time</th>
<th>II</th>
<th>ID</th>
<th>DD</th>
<th>P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>II v ID v DD</td>
<td>II v D+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=933)</td>
<td>Baseline</td>
<td>1699 (24)</td>
<td>1737 (17)</td>
<td>1712 (21)</td>
<td>0.370</td>
<td>0.298</td>
</tr>
<tr>
<td></td>
<td>Response</td>
<td>25.9 (1.1)</td>
<td>23.2 (0.7)</td>
<td>23.8 (0.9)</td>
<td>0.126, II v ID (p=0.044)</td>
<td>0.047</td>
</tr>
<tr>
<td>No CEI (n=688)</td>
<td>Baseline</td>
<td>1723 (28)</td>
<td>1753 (19)</td>
<td>1731 (25)</td>
<td>0.634</td>
<td>0.499</td>
</tr>
<tr>
<td></td>
<td>Response</td>
<td>27.3 (1.2)</td>
<td>23.5 (0.8)</td>
<td>24.3 (1.1)</td>
<td>0.039, II v ID (p=0.011)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, height, weight, angina or dyspnea in daily activities, previous smoking habits, myocardial infarction, CABG, PTCA and claudication. § Adjusted for age, sex, height, weight, training dosage, baseline performance, angina or dyspnea in daily activities, family history of CAD, previous or current smoking habits, resting DBP, intake of molsidomine, diuretics or digitalis, exercise-induced ST depression, myocardial infarction, CABG and claudication. P-value of the ANCOVA and, where required, results of the post-hoc comparison are presented. Values are means (SE). CEI=conversion enzyme inhibition.
Acknowledgements

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Competing interest statement
There is no conflict of interest.

Ethics approval
Approval for this study was obtained from the Ethics Committee of the Faculty of Medicine.

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References


