
Running head: ACE gene and aerobic power in CAD

J Defoor*, L Vanhees*†, K Martens‡, G Matthijs†, A Van Vlerken*, D Zielinska§, D Schepers*, R Vlietinck‡, R Fagard†

*Cardiovascular Rehabilitation Unit, Department of Rehabilitation Sciences, †Hypertension and Cardiovascular Rehabilitation Unit, Department of Molecular and Cardiovascular Research, ‡Centre for Human Genetics of the University Hospitals Leuven, Department of Human Genetics, K.U.Leuven, Belgium, §Department of Rehabilitation, Medical University of Gdansk, Poland.

Address for correspondence:
Prof. Dr. Luc Vanhees Phone: 32-16-329005
Head Department Rehabilitation Sciences Fax: 32-16-329197
Tervuursevest 101 E-mail: Luc.vanhees@faber.kuleuven.be
B-3000 Leuven, Belgium

Keywords:
Cardiac Rehabilitation, Angiotensin, Exercise, Genetic, Oxygen Uptake
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] Intron 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 (CArdiac 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 vs women frequencies of the I- and D-allele (0.47 vs 0.41 and 0.53 vs 0.59, respectively) and of the II, ID and DD genotype (0.23 vs 0.18, 0.47 vs 0.46 and 0.30 vs 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 vs ID patients and vs 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 II v ID v DD</th>
<th>P value II v D+</th>
</tr>
</thead>
<tbody>
<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>Response §</td>
<td>25.9 (1.1)</td>
<td>23.2 (0.7)</td>
<td>23.8 (0.9)</td>
<td></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>Response §</td>
<td>27.3 (1.2)</td>
<td>23.5 (0.8)</td>
<td>24.3 (1.1)</td>
<td></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

This study was supported by grants from the Fund for Scientific Research – Flanders, Belgium (F.W.O., Grant G.0124.02) and from the Research Council of the University of Leuven, Belgium (Grant OT/01/46). We thank Prof. E. Legius, Department of Human Genetics, K.U.Leuven, Belgium, for his valuable advice. J. Defoor is Research Assistant of the Fund for Scientific Research – Flanders, Belgium. L. Vanhees is holder of the Faculty Chair ‘Health and Lifestyle’ of the Faculty of Health Care, University of Professional Education, Utrecht, The Netherlands.

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.

Copyright statement
The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its licensees to permit this article to be published in HEART editions and any other BMJPGL products to exploit all subsidiary rights, as set out in our licence (http://heart.bmjjournals.com/misc/ifora/licenceform.shtml).

References


The CAREGENE study: ACE Gene I/D polymorphism and effect of physical training on aerobic power in coronary artery disease

Johan Defoor, Luc Vanhees, Kevin Martens, Gert Matthijs, Anke Van Vlerken, Dominika Zielinska, Dirk Schepers, Robert Vlietinck and Robert Fagard

*Heart* published online August 5, 2005

Updated information and services can be found at:
[http://heart.bmj.com/content/early/2005/08/05/hrt.2004.054312.citation](http://heart.bmj.com/content/early/2005/08/05/hrt.2004.054312.citation)

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**

Articles on similar topics can be found in the following collections

- Drugs: cardiovascular system (8842)
- Hypertension (3006)
- Acute coronary syndromes (2742)
- Diabetes (842)
- Interventional cardiology (2933)
- Percutaneous intervention (964)
- Tobacco use (635)

**Notes**

To request permissions go to:
[http://group.bmj.com/group/rights-licensing/permissions](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to:
[http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to:
[http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)