Angiotensin-Converting Enzyme Genotype Interacts With Systolic Blood Pressure to Determine Coronary Heart Disease Risk in Healthy Middle-Aged Men

Amal Muthumala, Hugh Montgomery, Jutta Palmen, Jackie A. Cooper, Steve E. Humphries

Abstract—The impact of the ACE I/D polymorphism on coronary heart disease (CHD) risk is modest at most, however it may act as a modifier gene. ACE genotype was determined in 2711 healthy middle-aged men (mean age 56 years) followed for 15 years. No genotype-CHD risk association was found, but when analyzed by quartiles of systolic blood pressure (SBP), compared with II homozygotes, carriage of each additional D allele was protective at lower SBP, but in the highest quartile (SBP > 150 mm Hg) conferred almost 1.5 times the risk for CHD (genotype interaction $P=0.003$). When SBP was analyzed as a continuous variable, again a highly significant association was seen, with the hazard ratio ([95% CI]) for a 1 SD increase in SBP being 0.90 [0.70 to 1.15] for IIs and 1.40 [1.21 to 1.61] for ID/DD (genotype SBP interaction $P=0.002$). The D allele was protective against CHD at lower SBP but would overtake the II risk at higher SBP. In hypertension, the proinflammatory or prohypertrophic properties of angiotensin II may explain this association. The LPL S447X polymorphism also impacts on CHD risk through interaction with hypertension, and there was an additive action of these 2 polymorphisms and SBP on CHD risk (hazard ratio for 1 SD increase in SBP for combined genotypes 1.78 [1.30 to 2.45]). Thus in the presence of hypertension, common variation in “modifier” genes confers significant CHD risk. (Hypertension. 2007;50:348-353.)

Key Words: systolic ■ risk factors ■ genetics-association studies ■ ACE gene ■ CHD ■ hypertension

As a key component of the human endocrine renin-angiotensin system (RAS), angiotensin-converting enzyme (ACE) converts angiotensin I to pressor angiotensin II (Ang II), and degrades vasodilator kinins. However, local tissue RAS exist in diverse tissues including the human arterial vascular wall, where they modulate growth and inflammatory responses. As such, tissue ACE represents a good candidate as a mediator of coronary heart disease (CHD).

The absence (deletion, D allele) rather than the presence (insertion, I allele) of a 287-bp fragment in intron 16 of the ACE gene is associated with elevated ACE activity both in the circulation and in tissues. As such, one might anticipate the ACE D-allele to be associated with excess CHD risk. Cambien et al were the first to report such an observation. Results from subsequent studies, however, have proved less consistent, and metaanalysis of published data suggest the impact of ACE genotype on myocardial infarction (MI) risk to be modest (relative risk associated with DD genotype of approximately 1.27). Such inconsistency and weakness of effect may, however, reflect the interaction of ACE genotype with environmental factors in determining risk. Indeed, accruing evidence suggests that the ACE gene may modulate the development of complex phenotypes through interaction with stimuli such as smoking, where the D-allele seems associated with higher cardiovascular disease mortality. An interaction with blood pressure may also exist, the D-allele being associated with a higher risk of heart failure among hypertensives.

We therefore hypothesized that ACE genotype might interact with SBP to determine CHD risk. We tested this hypothesis in the Second Northwick Park Heart Study (NPHSII), which offers 15-year prospective follow-up study of middle-aged men healthy at enrollment. We have previously observed that a common functional variant in the gene for lipoprotein lipase (LPL)—the S447X polymorphism—does interact with SBP on CHD risk. For this variant, increasing blood pressure had a greater effect on risk in X447 allele carriers than in S447 homozygotes. In view of this similar pattern of gene-blood pressure interaction, the combined effects of the ACE ID and LPL S447X and SBP on CHD risk were also determined.

Methods

Subjects comprising those recruited from the prospective Second Northwick Park Heart Study (NPHSII), described in detail elsewhere. In brief, 3012 unrelated healthy white middle-aged male subjects were recruited from 9 United Kingdom general medical practices throughout the UK and prospectively followed for the
magnification using published primers and conditions for
leukocyte DNA polymerase chain reaction (PCR)
mercury sphygmomanometer after 5 minutes seated.
recorded. At entry, SBP was recorded twice with a random zero
history of MI and regular use of aspirin or other cardiovascular
development of CHD from 1989. Exclusion criteria included a
ACE Genotyping
TABLE 1. Baseline Characteristics by CHD in NPHSII Men With

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No CHD</th>
<th>With CHD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.0 (3.4)</td>
<td>56.6 (3.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>BMI,* kg/m²</td>
<td>26.2 (3.4)</td>
<td>26.7 (3.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>SBP,* mm Hg</td>
<td>136.7 (18.7)</td>
<td>141.4 (19.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>84.3 (11.4)</td>
<td>87.0 (11.4)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Smoking, % (n)</td>
<td>27.3 (666)</td>
<td>37.2 (100)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.7 (1.01)</td>
<td>6.0 (1.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglyceride,* mmol/L</td>
<td>1.7 (0.93)</td>
<td>2.0 (1.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrinogen,* g/L</td>
<td>2.7 (0.52)</td>
<td>2.8 (0.49)</td>
<td>0.003</td>
</tr>
<tr>
<td>CRP,* mg/L</td>
<td>2.4 (2.43)</td>
<td>3.26 (3.37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Genotype distribution II/DD/DD</td>
<td>579/1194/669</td>
<td>64/134/71</td>
<td>0.95</td>
</tr>
<tr>
<td>D Allele frequency</td>
<td>0.518</td>
<td>0.513</td>
<td>0.81</td>
</tr>
</tbody>
</table>

*Geometric mean (approx SD).

devlopment of CHD from 1989. Exclusion criteria included a
history of MI and regular use of aspirin or other cardiovascular
medications, including antihypertensive medication. CHD was
defined as MI (clinical or postmortem evidence), coronary revascular-
ization, or a new major Q wave on ECG. Time to first event was
determined by 2 independent technicians blind to subject
data. At entry, SBP was recorded twice with a random zero
mercury sphygmomanometer after 5 minutes seated.
DNA was available for 2782 eligible men. Genotypes were
determined by leukocyte DNA polymerase chain reaction (PCR)
amplification using published primers and conditions for ACE\textsuperscript{13} and
resolved using Microarray Diagonal Gel Electrophoresis (MADGE)
for approximately 87% of samples and using Taqman, primers, and
probes for rs4341 (in complete LD with the
ACE I/D polymorphism)
as described in Tanaka et al\textsuperscript{14} for the remaining samples. Genotype
determination was as expected for Hardy-Weinberg equilibrium. As
shown in Table 1 there was no significant difference between
those who developed CHD and those that did not in ACE
genotype distribution (P=0.95) or D allele frequency (P=0.81).
There was no significant difference in any risk factor between
the different genotype groups (not shown, all P>0.25), in
particular for SBP (P=0.97) and DBP (P=0.82).

Because SBP was an established risk factor for development
of CHD and there is evidence for ACE genotype SBP interaction
in other diseases, their interaction on 15-year risk of develop-
ment of CHD (adjusted for age and practice) was examined.
Figure 1 demonstrates analysis of CHD risk for D-allele carriers
by quartiles of SBP (additive model). In the lower 2 quartiles
there was a trend for a protective effect by the D-allele, with
thereafter a stepwise rise in risk for the D-allele,such that in the
highest quartile of SBP (\geq 150 mmHg), CHD risk of the
D-allele carrier was almost 1.5 times that of II homozygotes
by quartiles of SBP. In the lower 2 quartiles
there was a trend for a protective effect by the D-allele, with
thereafter a stepwise rise in risk for the D-allele carrier. Such a
result was seen with the dominant model for D-allele interaction (P value
0.004). When the results were also adjusted for cholesterol,
triglycerides, and smoking (classical risk factors for CHD
significantly different between cases and controls in NPHSII; see
Table 1), a similar pattern of association was seen (interaction
P value 0.004).

When SBP was examined as a continuous variable (Figure
2A), the HR for a 1 SD increase in SBP was 0.90 [0.70 to
1.15] for IIs and 1.4 [1.21 to 1.61] for ID/DD (genotype SBP
interaction P=0.002). Thus, compared with the common
multiplicative effects. Frequencies were compared by Chi-squared
test. Estimated probabilities were obtained from logistic regression
models and plotted to illustrate the increase in risk with blood
pressure. Additive effects were determined by fitting coding geno-
type according to the number of rare alleles carried.

Results

ACE genotype data were obtained in 2711 men (97% subjects
with DNA), whose baseline characteristics were not signifi-
cantly different from the whole group (not shown). After 15
years of follow-up, 269 men with ACE genotype had developed
CHD. Established risk factors were all associated with increased
risk of development of CHD (Table 1). The distribution of
genotypes was as expected for Hardy-Weinberg equilibrium. As
shown in Table 1 there was no significant difference between
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genotype distribution (P=0.95) or D allele frequency (P=0.81).

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D-allele carrier was almost 1.5 times that of II homozygotes
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with the dominant model for D-allele interaction (P value
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interaction P=0.002). Thus, compared with the common

SBP (mm Hg) ID/DD vs II

>150 506/78 vs 156/15

138-150 516/50 vs 153/13

125-137 524/38 vs 171/18

<125 520/39 vs 163/18

Figure 1. Hazard ratio for each additional
D allele by quartile of SBP. ID/DD (number
of controls/number developing CHD) vs II
(number of controls/number developing
CHD). Reference group is specific for
each SBP quartile—it is the ratio of num-
ber of individuals with II genotype who
develop CHD after 15 years to the total
number of II controls within the same
SBP quartile.
D-allele carriers (66.3% of men), who showed the expected effect of increasing CHD risk with increasing blood pressure, the ACE II men (23.7% of the group) were protected from this blood pressure risk effect. Additional adjustment for cholesterol, triglyceride, and smoking led to a very similar pattern with the HR for a 1SD increase in SBP being 0.85 [0.66 to 1.09] for IIs and 1.32 [1.14 to 1.52] for ID/DD (genotype SBP interaction P/H11005 0.002).

**Effect on Risk of Combined Genotypes**

The combined effects of the ACE I/D, LPL S447X, and SBP on CHD risk were examined. As shown by Talmud et al11 and in Figure 2B, increasing blood pressure had a greater effect on risk in X447 allele carriers than in S447 homozygotes (interaction significant in categorical analysis). 2665 men were successfully genotyped for both polymorphisms. When the men were grouped into LPL SS or SX/XX subjects, and stratified by ACE II or ID/DD groups (Table 2 and Figure 2C), the commonest genotype group of the ACE D-allele carriers who were also LPL SS homozygotes (61.3% of the men) showed the expected effect of increasing CHD risk with increasing blood pressure, with a HR for a 1SD increase in SBP of 1.31 [1.12 to 1.53], P=0.001. As would be predicted if the genotype risk effects were additive, the largest effect of increasing blood pressure on CHD risk was seen in the ACE D-allele carriers who were also LPL X-allele carriers (14.9% of the men) who had a HR of 1.78 [1.30 to 2.45] P=0.0001. By contrast, there was no evidence for a significant effect of increasing blood pressure in those with the ACE II and LPL SS or ACE II LPL SX/XX combined genotype, with the HR estimates for both of these groups being significantly lower than for their D-allele carrier counterparts (P=0.02 for both comparisons). These results demonstrate that a rise in SBP only leads to a significant rise in CHD risk with carriage of the ACE D-allele, with the risk being even greater in those who also carry the LPL X-allele. This association was maintained when also adjusting for cholesterol, triglycerides, and smoking (Table 3). A similar result was obtained when SBP was analyzed as a categorical variable (above and below median of 137 mm Hg). Carriers of the D allele and X allele

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**Figure 2.** A, Probability of CHD by SBP in NPHSII subjects stratified by ACE I/D genotype. ID/DD (number of controls/number developing CHD)= (1863/205); II (number of controls/number developing CHD)= (579/64). B, Probability of CHD by SBP in NPHSII subjects stratified by LPL S447X genotype. SX/XX (number of controls/number developing CHD)= (483/44); SS (number of controls/number developing CHD)= (2014/175)11. C, Probability of CHD by SBP in NPHSII subjects stratified by LPL S447X and ACE I/D genotype. (For number of samples see Table 2).
had a HR of 0.42 (P=0.02) compared with those with II and SS genotypes in the low risk environment (SBP <137 mm Hg), but in those with SBP >137mmHg, D and X allele carriers had a higher CHD risk compared with their II and SS counterparts with HR 1.60 (P=0.10).

Discussion

In view of the increasing evidence for the ACE gene acting as a modifier for cardiovascular disease,9,10 we set out to test the hypothesis that prospective CHD risk would be influenced by a significant risk factor for CHD, SBP. As expected, no overall genotype risk association was found, but analysis by quartiles of SBP revealed a differing genotype CHD risk based on SBP, and possession of the D allele was associated with higher risk when SBP was elevated. There is a precedent for such a proposed interaction: among hypertensive subjects, those carrying the ACE D-allele have been reported to be at higher risk of heart failure.10

This impact of the ACE I/D polymorphism, and its interaction with SBP in determining CHD risk, is likely to depend on associated differences in tissue ACE activity4,5 and consequent Ang II generation. Ang II is a vasoconstrictor and causes oxidative stress in endothelium (and myocardium) via NADPH oxidase which causes endothelial dysfunction and smooth muscle cell proliferation.15 It activates the recruitment of inflammatory cells to injured arteries,16 and can upregulate adhesion molecules and chemokines17,18 causing lymphocyte and monocyte adhesion to the endothelial surface promoting atherosclerosis. ACE may also promote atherosclerosis through inactivating bradykinin, a vasodilator with antifibrinolytic properties.19

Whatever the mechanism, ACE inhibition reduces CHD event rate among patients with vascular disease.20 On the other hand, hypertension activates vascular RAS21,22 causing oxidative stress, which leads to the development of endothelial dysfunction and atherosclerosis.23 This is probably a vicious cycle, with endothelial injury perpetuating further RAS activation.16 Such data are also in keeping with other observations. Ang II drives cardiac hypertrophy, partly through the generation of oxidative stress via NADPH oxidase.24,25 Given that the ACE D-allele is associated with a greater left ventricular (LV) growth response to a variety of stimuli26–28 including hypertension,29 and that exuberant LV growth is independently associated with excess CHD risk,30,31 an interaction of ACE with SBP in determining CHD risk would appear entirely logical. Therefore the D allele may be proinflammatory or prohypertrophic or both in hypertensive but not in normotensive subjects.

Although a lack of vascular RAS activation might have accounted for the absence of detrimental impact of the ACE D-allele on CHD risk among those with lower SBP, the suggested protective effect of the D-allele in this group remains unexplained. One might postulate that other factors are at work: the D allele may be associated with improved insulin sensitivity,32 and a mouse model has suggested that greater ACE expression was associated with less weight gain.33 It is certainly unclear why a high ACE state may confer a benefit in the context of low blood pressure. Rather than a definitive benefit in this situation, it may be more probable that there is a lower risk without the presence of high blood pressure. For Ang II to have a damaging effect it may need to be in the setting of hypertension, where endothelial dysfunction or cardiac hypertrophy have already been instigated. In the context of normotension where there is no raised tissue stress, there may be less substrate for raised Ang II levels (eg, lower angiotensin II receptor type I density) therefore lower CHD risk. Whatever, the effect does not seem to have occurred by chance, being evident in both lower quartiles of SBP.

Analysis of the SBP interaction with 2 gene polymorphisms suggests that only in the presence of a harmful environment (eg, hypertension) do their common variants become disease-modifying. Further analysis suggests that the combination of the 2 risk gene variants in the risk environment leads to an even higher risk (but no more than expected). The raised LPL activity in both lower quartiles of SBP.

<table>
<thead>
<tr>
<th>ACE I/D LPL S447X (No. of Controls With Both Genotypes/No. of CHD Cases With Both Genotypes)</th>
<th>HR for 1 SD Increase in SBP (95% CI)</th>
<th>P Value (Adjusted for Age and Practice)</th>
<th>Interaction ACE (I/D)xLPL S447XxSBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>II SS (460/54)</td>
<td>0.87 (0.67–1.14)</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>SX/XX (110/9)</td>
<td>0.60 (0.29–1.44)</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>ID/DD SS (1467/167)</td>
<td>1.22 (1.04–1.44)</td>
<td>0.02</td>
<td>P=0.11</td>
</tr>
<tr>
<td>SX/XX (362/36)</td>
<td>1.69 (1.23–2.32)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>
from the X allele of LPL S447X leads to a greater fatty acid availability and we have suggested,11 in the context of myocardial and vascular stress eg, hypertension, this will be detrimental, leading to vascular dysfunction or greater LVH, again leading to a higher CHD risk. The greater LVH or higher inflammatory stress from both gene variants acting together may in some patients lead to a multiplicative interaction on risk, but this was not demonstrated in this group of healthy subjects. Further studies to examine this in patients, for example with heart failure, would be of interest.

At recruitment no subjects were taking ACE inhibitors, Ang II receptor blockers, Beta receptor blockers, or statins. Adjustment for antihypertensive medication use would be helpful, but these data are unavailable for this prospective study based in general practice. Although adjusting for antihypertensive use might strengthen the conclusions, the lack of information is unlikely to confound the results. If there was a difference in incidence or treatment of hypertension in men by ACE genotype, this would be a potential confounder. This would occur if the ACE I/D polymorphism were associated with significant effects on SBP or DBP, however there is no strong evidence for such an association in the literature, and no evidence for a difference in mean SBP or DBP by ACE genotype in NPHSII men at baseline. Although there is some published evidence to suggest that subjects with essential hypertension with different ACE genotype may respond differentially to treatment with different antihypertensive medications, unless hypertensive subjects with different ACE genotype were treated with different medication, which seems implausible, the reported genotype–medication interactions are unlikely to be a confounder of the associations we see with CHD events.

It is interesting to note (from Figure 2A) that in men with a SBP of below 140 mm Hg, when it is likely that no antihypertensives were being used in this cohort, the CHD risk of carrying the D allele increased with rising SBP as opposed to carriers of II genotype. This would argue against use of antihypertensives confounding the results seen. Furthermore, although those who did develop hypertension may have been treated, it seems despite this, the CHD risk for individuals with the D allele and II genotype remained distinct, and continued as would be predicted.

It is important to note that treatment after CHD event would not confound these results because survival is only recorded up to the event. Furthermore, in the UK, hypertensive middle-aged males asymptomatic for CHD would certainly have been in the minority with regard to adequate treatment, especially throughout the 1990s. The use of antihypertensives in this population, especially ACE-inhibitors, would have been low. There is certainly no consistent pharmacogenetic interaction between ACE-inhibitors (and other antihypertensives) and outcome in hypertensive subjects in a recent comprehensive review.34

Another assumption is that these associations are explained by differing levels of ACE by ACE (I/D) genotype. To confirm this, measurement of plasma ACE levels would have been useful to look for correlation with genotype and levels, and levels and risk, but these measurements had not been made. However, there are strong and consistent published data which demonstrate that ACE levels in subjects with the ACE D allele are significantly higher than those with the I allele,4,5 and this effect remains the most likely direct mechanism.

It is of note that the mean baseline SBP levels in those that remained CHD free (mean 136.7 mm Hg for mean age of 56 years) was substantially higher than in the comparative group in the Framingham Heart Study (mean SBP of 129.2 mm Hg for mean age of 58 years). The explanation for this is not clear, and may be methodological or attributable to the 2 groups having different genetic and environmental factors. However, the mean SBP in this group of healthy men is representative of the UK, because compared with national figures (Department of Health, Health Survey of England [2003] http://www.dh.gov.uk/assetRoot/04/09/89/15/04098915.xls), the mean SBP in men in England in age groups 45 to 54 in 1993 and 1994 (the last 2 years at which recruitment occurred in NPHS2) were 138 mm Hg and 136 mm Hg, respectively.

Perspectives

The demonstration of gene environment interaction in the pathogenesis of complex phenotypes is increasingly prevalent, especially with the strength of prospective studies.35 This is the first study to show interaction between the ACE gene and SBP in determining prospective risk of CHD, but replication is required to confirm these findings with appropriate pharmacogenetic evaluation.

Acknowledgment

We acknowledge the contributions of the late Professor George Miller, the PI of the NPHSII study, to this work.

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Disclosures

None.

References


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