Letters to the Editor

ACE-Gene Polymorphism and Endothelial Dysfunction in Normal Humans

To the Editor:

Recently, Butler et al.¹ have reported that the DD angiotensin-converting enzyme (ACE) genotype in a young normal population is associated with a blunted vasodilator response both to acetylcholine (ACh) and sodium nitroprusside. These data disagree with findings previously reported by ourselves.² In fact, in our article, we demonstrated that hypertensive patients with the DD genotype are characterized by significantly less endothelium-dependent vasodilation in comparison with ID and II genotypes, but normal control subjects with a DD genotype had similar endothelium-dependent vascular responses when compared with the non-DD genotypes.

Moreover, no significant differences were observed in endothelium-independent vasodilation between normal subjects and hypertensive patients. Similarly, no significant differences were detected when we subdivided the control and hypertensive groups according to ACE-gene genotypes. Methodological differences and population selection criteria may explain the following disparate findings:

(1) The authors demonstrated both an impaired endothelium-dependent (ACh) and an endothelium-independent (nitroprusside) vasodilation. These data are in opposition to results reported by many authors who demonstrated, obviously, any difference in endothelium-independent vasodilation between normal controls and patients with endothelial dysfunction due to hypertension, diabetes, aging, etc. In fact, nitric oxide induces vasodilation by stimulating the activity of soluble guanylate cyclase within the vascular smooth muscle, thereby elevating tissue levels of cyclic GMP. On the other hand, sodium nitroprusside induces endothelium-independent vasodilation through the same effector pathway by providing an inorganic source of nitric oxide. When authors postulate that endothelium-independent vasodilation is also blunted, they affirm that in normal controls c-GMP function is also influenced by ACE gene polymorphisms. Thus, the ACh effects on endothelial function is affected by c-GMP dysfunction and, obviously, all data could be revised according to this new finding.

(2) The ACh doses used by Butler et al. are lower than those employed by Panza et al.³ Creager et al.⁴ and ourselves.²,⁶ It is improbable that doses employed by Butler can induce significant differences between genotypes in dose-response curves.

(3) In the study group, 29 subjects (43.2%) are smokers; therefore, these subjects cannot be considered normal because it has been demonstrated that smoking is associated with impaired endothelium-dependent vasodilation.⁷ These evidences are partially confirmed by data shown by Butler himself; in particular, he observed a significant difference during ACh infusion in II and DD smoker groups.

Moreover, we observed other unclear differences obtained by analysis of data between normal controls and smokers.

(a) Vascular response of norepinephrine was significantly higher only in II smokers than in non-smokers. The authors did not postulate any explanation of these results.

(b) The values of flow ratio after L-NMMA infusion were significantly different in II and ID smoker groups, while they were not different in smokers and nonsmokers with the DD genotype. We are in agreement with the authors, who postulated that their results can be influenced by methodological design.

(c) The statistical analysis did not state if the smokers influenced the flow ratio; thus, a multivariate analysis is probably necessary.

Nevertheless, data reported by Butler et al. in nonsmoker subjects are similar to those obtained in our normal population, as well. In fact, if we analyze the vascular response to ACh (Table 2 in Butler’s paper) in nonsmoker subjects subdivided for genotype, no significant differences are detectable (P=0.166 by ANOVA).

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Response

We would like to thank Drs Perticone and Ceravolo for their interest and subsequent letter. We will answer each of their points in turn.

We demonstrate impaired NO-induced vasodilation by both endothelial-dependent (ACh) and -independent (nitroprusside) pathways. We cannot comment on the cellular mechanism for this finding based on study. However, our group has previously shown that nitroprusside responses can be improved (by ACE inhibitors in hypercholesterolaemia) along with an expected improvement in endothelial dependent responses. It is possible that NO at endothelial cell level (whatever its original source—ACh or nitroprusside) is degraded by free radicals and or angiotensin II. It may be that cGMP is not affected at all and that NO is removed prior to its effect on soluble guanylate cyclase.

We accept that our doses may be slightly lower, but we can demonstrate significant differences between genotypes.

The point that concerns differences between endothelial function in smokers and nonsmokers is well established. If we analyze our data, irrespective of genotype, we see that smoking was still associated with a significant impairment in endothelial-dependent vasodilatation to acetylcholine with values of 4.07 ± 2.18 and 3.42 ± 1.79 in the nonsmoking and smoking
groups, respectively ($P=0.03$; 95% CI 0.004, 0.283). There was no significant difference between endothelial-independent vaso- dilators: sodium nitroprusside ($2.61 \pm 1.19$ versus $2.43 \pm 1.32$; $P=0.20$, 95% CI $-0.16$, 0.04) and verapamil ($4.87 \pm 3.44$ versus $4.74 \pm 3.56$; $P=0.51$, 95% CI $-0.22$, 0.12). Smokers showed a significant impairment in endothelial-dependent vasoconstriction; monomethyl-L-arginine ($0.78 \pm 0.22$ versus $0.87 \pm 0.21$; $P=0.005$, 95% CI 0.01, 0.08). The corresponding figure for norepinephrine just failed to reach statistical significance ($0.61 \pm 0.20$ versus $0.68 \pm 0.17$; $P=0.07$, 95% CI 0.01, 0.28).

Dr Perticone expresses particular interest in the norepinephrine result. Although our data are not conclusive, they are suggestive that there is a degree of blunting of the response to noradrenaline. The explanation may be due to downregulation of $\alpha$ adreno-receptors by endogenous catcholamines because long-term smokers may have increased plasma levels of noradrenaline.$^{2,3}$

The final point is a little difficult to understand as Dr Perticone cannot have reanalyzed our data in this manner without our raw data. Even when eyeballing Table 2 in our paper, quite a difference between II ($4.9 \pm 2.5$) versus DD ($3.3 \pm 1.4$) genotypes in nonsmokers is evident.

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