ACE Gene Polymorphism and Coronary Artery Disease
A Question of Persuasion or Statistical Confusion?

“...in the intermediate phase, swiftly developing complexity within the system hides the risk of imminent chaos. But the risk is there.”

Michael Chrichton’s The Lost World

Great personal enthusiasm, temptation, technical efforts, and complex mathematical equations characterize the developing research field of newly identified gene polymorphisms and their impact on a variety of cardiovascular diseases. After the first publication of Cambien and coworkers in Nature in 1992, who reported that the IDD angiotensin-converting enzyme (ACE) polymorphism is a potent risk factor for myocardial infarction, great enthusiasm emerged that a potentially new class of risk factors was identified. In the following years, researchers repeatedly tried to prove with controversial results that a single-gene polymorphism, such as the ACE polymorphism, is associated with a higher risk of myocardial infarction, for example. Much to their surprise, different populations apparently responded differently with regard to the appearance and overall impact of the ACE polymorphism on myocardial infarction. One of the potential answers is related to the composition of polymorphisms in different study populations. Whereas Cambien et al analyzed a population in which ≈50% were ACE DD carriers, the distribution of this polymorphism was found to be only ≈23% in normal Western populations.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Agerholm-Larsen and coworkers report results from a meta-analysis of the ACE gene polymorphism studies with respect to plasma ACE activity, blood pressure, and the risk of myocardial infarction. The authors compared, in their analysis, large-scale studies with smaller regional cohorts. This meta-analysis included 46 smaller and larger studies and a total number of 32,715 white subjects. Although the authors report that plasma ACE activity was increased in ID or DD ACE phenotypes compared with the IH polymorphism, they failed to show an association with increased risk of myocardial infarction, ischemic heart disease, or cerebrovascular disease. Since 3 previously published meta-analyses reported a positive association, the question can be raised as to why the authors of the current report did not detect any positive association. Is their conclusion based on a statistical artifact, or is the result of this particular meta-analysis the ultimate correct answer? Compared with other meta-analyses, very restrictive inclusion parameters were applied before the statistical analysis, leading to the exclusion of a variety of positive studies. Moreover, the authors selected only those studies that reported a complete set of parameters including plasma ACE activity and blood pressure. Are these inclusion criteria correct? So far, it has never been shown that a particular ACE polymorphism directly causes an increase in ACE activity. However, studies by Rigart et al and Schunkert et al reported that patients with the IID and ID/D ACE polymorphisms have elevated levels of plasma and myocardial ACE activity, indicating that ACE activity is a crucial marker for the characterization of populations with regard to ACE polymorphisms.

Given the enormous number of studies that support the concept that blocking ACE by ACE inhibitors is beneficial for patients with hypertension, congestive heart failure, and possibly, coronary artery disease, it is our understanding (and persuasion) that the ACE DD polymorphism contributes to the overall risk of developing a myocardial infarction rather than trying to prove this concept. It seems naive to expect that by combining heterogeneous study populations from around the globe and calculating a meta-analysis one could identify the impact of a single polymorphism (only 260 bp in the human genome) on the risk of myocardial infarction, especially since polymorphisms are characterized by an undefined phenotype compared with gene mutations.

Thus, the question remains whether or not we should believe that a single-gene polymorphism is associated with a higher risk of myocardial infarction and if so, how do we prove this concept. Coronary artery disease is a multifactorial disease. Many environmental and potentially, genetic factors contribute to the development of a clinical event, such as myocardial infarction. Each of the underlying risk factors, such as LDL cholesterol or homocysteine, is also multifactorial and polygenic. Therefore, for any individual, variations at different gene loci will interact with different environmental factors to determine their overall risk of myocardial infarction. Moreover, the age and duration of environmental influence on the individual seem to play an important role. All of the previous studies enrolled adults. Observations in large cohorts of apoE4-positive infants, however, have demonstrated that the harmful influences of environmental factors, eg, of a Western diet, start as early as 7 to 8 month postpartum. Thus, it seems odd nowadays to summarize heterogeneous populations of different ages and calculate their risk for myocardial infarction. By doing so, we compare smaller study cohorts, which are characterized by regional...

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This work is dedicated to the 65th birthday of Hermann Schieffer, MD, Department of Cardiology and Angiology, Universität des Saarlandes, Homburg/Saar, Germany.

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environmental influences (e.g., Mediterranean diet, physical activity) with large-scale, multicenter studies with heterogeneous populations (e.g., the World Health Organization–sponsored MONICA survey). Population and field genetics in *Drosophila melanogaster* and other species taught us to compare only those individuals with absolutely identical mutations or polymorphism. In contrast to these species, we do not yet know our complete genome.

Taken together, the results from the current meta-analysis seem convincing and expected. The negative results underline the concept that other important factors (genetic or environmental) overcome the overall impact of 1 particular polymorphism, e.g., the ACE D/D polymorphism. Thus, any specific polymorphism will have only a small, nonsignificant effect on risk in the overall population. However, there will be highly selected subgroups (i.e., young age) in which the ‘risk’ will be detectable and the effect of the polymorphism will be greatly exacerbated. Therefore, the ‘risk’ associated with the polymorphism will be clinically important only in some subjects who carry a certain genetic risk profile. The critical genetic code that predicts the individual risk is not completely known.

However, as stated above, we would predict that any common polymorphism in the population will have only a minor effect on the level of the specific risk factors. In the year 2004, however, the Human Genome Project will be completed. By that time, all genes will be identified, and early on, a variety of polymorphisms will be identified that may have an impact on cardiovascular diseases. By that time, we may be able to discriminate between environmental risk and genetic risk for, e.g., the development of myocardial infarction. The specific individual genetic risk for myocardial infarction will then be potentially calculable based on a genomic analysis.

We are currently in the intermediate phase of genetic/genomic investigations. Retrospective analysis and reevaluation of previous observations from controversial studies may confuse our colleagues and patients and may misguide potential beneficial therapeutical interventions. Each individual human being with his or her specific genes has an individual risk of developing a cardiovascular disease, e.g., a myocardial infarction. With the knowledge of a completely identified human genome, researchers will more and more realize that gene polymorphisms in symphony (interaction and interplay) will lead us to the individual risk of our patients. Thus, at the moment, retrospective analysis of heterogeneous populations may not be capable of clarifying the question as to whether the ACE polymorphism is an independent risk factor for the development of a myocardial infarction. Clearly, further work is needed when we know our genetic code. With the help of newly developed techniques, it will be quite likely that the role of gene polymorphisms for the development of cardiovascular diseases can be identified.

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