Editorial

Should the contribution of ACE gene polymorphism to left ventricular hypertrophy be reconsidered?

Why some individuals and not others develop left ventricular hypertrophy (LVH) in the face of hypertension remains a mystery. What is certain is that none of us would wish to develop it ourselves. Even among asymptomatic normotensives with LVH, not only are cardiac morbidity and mortality raised, but too often are the risks of suffering coronary, peripheral, or cerebrovascular disease.

And herein lies a second mystery: why should a thicker left ventricular wall predispose to increased risk of coronary or cerebrovascular disease? Evidently, understanding the mechanisms regulating myocardial growth might shed light on the pathophysiology of the hypertensive state, leading to new therapeutic strategies.

Myocardial tissue renin-angiotensin systems and myocardial growth

Most of us are familiar with the role of the circulating or endocrine renin-angiotensin system in the control of circulating blood volume and blood pressure. Fewer will be familiar with the recognised role of local renin-angiotensin systems in controlling growth responses in diverse tissues. Could they be performing this function in the mammalian heart? Certainly, renin-angiotensin system components are synthesised locally in LV tissue, and such synthesis is upregulated during ventricular growth. Angiotensin converting enzyme (ACE) inhibitors may be more effective than other agents at causing regression of hypertensive LVH, and may achieve this (as they do in animal models) without effect on blood pressure; but how could such a role for the myocardial renin-angiotensin system activity be further investigated? After all, left ventricular myocardial tissue cannot routinely be obtained for quantitative assessment of renin-angiotensin system gene expression.

In 1990, Rigat et al offered a way around this impasse. He described a polymorphism of the human ACE gene consisting of the presence (insertion, I allele) or absence (deletion, D allele) of a 287 base pair fragment. The D allele was associated with higher circulating and myocardial ACE concentrations. If the myocardial tissue renin-angiotensin system was a key regulator of LVH, then the D allele ought to be associated with greater LV mass.

Sadly, if the hypothesis was straightforward, the results were not. An initial wave of enthusiasm was rapidly followed by a wave of scorn.

Lack of association of ACE I/D genotype with LV mass

On the face of it, the report by Hamon and colleagues in this issue adds another nail to the coffin. In accord with a number of similar studies, no association between ACE genotype and LV mass was identified among 141 white patients with normal coronary arteries. Following a similar report by Lindpaintner et al, who studied 2439 individuals, it would seem hard to exhume the hypothesis.

Investigating the influence of a gene on a phenotypic trait, however, can be a tricky business. Only in the simplest of cases can polymorphisms be readily associated with phenotype. If the number of fingers were coded for by one gene, the association of a polymorphism with the presence of six fingers on each hand would be easy to spot—a rare phenotypic trait is easily associated with a rare allelic variant. But what if the phenotypic trait was a continuous rather than a discrete variable, if the polymorphism was common and accounted for only part of the phenotypic variation, and if phenotype was also strongly influenced by environment? The situation would be further confused if carriage of the polymorphism increased mortality, and study design would be hampered if the strength of influence of the polymorphism on phenotype was unknown.

All of these problems apply to the ACE gene I/D polymorphism. The polymorphism is ubiquitous (the genotypes II, ID, and DD divided roughly 1:2:1); LV mass is a continuous variable, under the influence of a large number of environmental and biological effects (for example, exercise, age, sex, blood pressure burden, race); the polymorphism may be associated with excess mortality (from ischaemic heart disease or cardiomyopathy), as is its presumed associated phenotypic trait (LVH); and the strength of influence of the polymorphism on LV mass is unquantified.

To identify an effect of a polymorphism such as this on phenotype would require a highly homogeneous young population, and minimal and quantifiable exposure to environmental influences on phenotype. A very large (and unpredictable, given the unknown strength of gene effect) number of subjects would be required, especially as ACE genotype accounts for only half of the variance in serum ACE concentrations; even if LV mass were linearly related to ACE concentrations, there would not be a perfect correlation between LV mass and ACE genotype. To date, no published study has met these criteria.

Hamon and colleagues' study, like others before, may be too small to detect an influence on LV mass. Nonetheless, a very powerful influence of ACE genotype on LV mass might be detectable in a highly uniform study population missing from these studies. Hamon et al, like others, studied a group of mixed sex (67% male) and diverse age (53 ± 10 years) among whom lifelong physiological effects on LV mass are unlikely to have been uniform, and which are not quantifiable. Nearly half (46%) the subjects suffered hypertension (or were treated for it, some with blood pressures of >160/95 mm Hg), the duration, severity, and influence of which is unknown.
Further, between 28% and 61% were receiving treatment of unknown duration with antihypertensive medications known have an effect on LV mass. Indeed, 12% were taking inhibitors of the gene product under investigation (namely, ACE inhibitors). These problems are not unique: between 12% and 16% of each genotype studied by Lindpaintner et al were similarly medicated. In studies of trait analysis, it is not possible to make any meaningful allowance for the influence of such factors on LV mass. Finally, lack of racial homogeneity in some studies might further hinder detection of a genotype-phenotype association. Both propensity to develop LVH (greater among blacks) and association between ACE genotype and ACE concentrations (perhaps low or absent among blacks) differs by race. Racial differences might partly account for the negative findings of Hamon and colleagues (using a white population), the negative findings of Lindpaintner et al (using mixed races), and the positive findings of Iwai et al (in a Japanese group).

All of these studies may have been prone to skew from several opposing factors: deaths attributable to the genotype or to LVH itself may have “filtered out” cases in which LVH was present, while strongly associated with LVH; in contrast, the effect of hypertension on LV mass might be amplified among those with the DD genotype; together, these factors would tend to increase study “white noise”, as would well recognised technical problems causing misclassification of some heterozygote subjects as being homozygote for the D allele.

Are reports of the hypothesis’s death premature? Perhaps we have all been trying to answer the wrong question. The issue, perhaps, is not whether the D polymorphism of the ACE gene is “the gene for LVH”. LVH is not a discrete phenotypic characteristic due solely to the presence of one gene. In fact, LV mass is a continuous variable and is generally a manifestation of an interaction between physiological stimuli (such as increased cardiac work) and a transducing system (possibly renin-angiotensin). Cross-sectional population-based studies may not be the most appropriate way to investigate such mechanistic issues. If myocardial tissue renin-angiotensin system transduces a growth stimulus, it is scarcely surprising that small studies of individuals exposed to minimal (and varied) growth stimuli fail to show an association of ACE genotype with LV mass. Neither is it a surprise that very large studies of heterogeneous samples exposed to diverse and unquantifiable growth stimuli generate sufficient white noise to mask any possible genotype associations. Comparative studies of individuals matched for ACE genotype, with one group exposed to an LV growth stimulus such as hypertension or physical training, or prospective studies of individuals of defined genotype in whom LV growth is anticipated are required. As a “second best”, one might examine studies that have included large numbers of individuals exposed to another genetic or environmental LV growth stimulus. Such stimuli, one might hypothesise, would be transduced more in those with increasing numbers of D alleles. From such studies comes the suggestion that ACE genotype might indeed be influencing LV mass. Among 183 patients with hypertrophic cardiomyopathy, DD genotype was associated with greater LV mass. D allele frequency was also higher among those with evidence of hypertrophic cardiomyopathy than in unaffected siblings. The association of systolic blood pressure with LV mass might be stronger in those of DD genotype. Finally, the D allele was more frequent among hypertensives and normotensives with ECG criteria for LVH than in those without. An association of ACE genotype with LV mass has been identified in LVH (greater among whites) and in some larger studies of untreated hypertensives, and DD genotype was associated with increased concentric remodelling in untreated patients referred for investigation of suspected arterial hypertension.

Although the place of the ACE gene I/D polymorphism is unclear, largely because of the lack of appropriate studies, the likely importance of tissue renin-angiotensin systems in the control of myocardial growth remains. Further investigation may yet have much to offer. Why a thicker LV wall should really be interpreted as an increased risk of coronary or cerebrovascular disease is another mystery. Reports linking ACE genotype (as a marker of tissue renin-angiotensin system activity) with risk of myocardial infarction, development of LVH and thickening of the common carotid arterial wall, might provide one explanation.

HUGH MONTGOMERY
Research Fellow, Hunter Institute for Cardiovascular Studies, Department of Cardiology, University College Hospital, Gray’s Inn Road, London WC1E 6DB, United Kingdom

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H. Montgomery

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