Correspondence. Letters to the Editor must not exceed 400 words in length and must be limited to three authors and five references. They should not have tables or figures and should relate solely to an article published in Circulation within the preceding 12 weeks. Authors of letters selected for publication will receive prepublication proofs, and authors of the article cited in the letter will be invited to reply. Replies must be signed by all authors listed in the original publication. Please submit three typewritten, double-spaced copies of the letter to Herbert L. Fred, MD, % the Circulation Editorial Office. Letters will not be returned.

Tumor Necrosis Factor-α and Interleukin-10 Genotypes in Congestive Heart Failure
To the Editor:
The allelic case-control study by Kubota et al1 suggests that polymorphisms at positions −308 and +252 of the tumor necrosis factor-α (TNF-α) gene do not influence either risk of heart failure or plasma levels of TNF-α for patients with heart failure. The investigators recognize the potential biases of patient selection inherent in the study and suggest that patients homozygous for TNFA2 or TNFB2 could have had a more “malignant” clinical course such that mortality was high before presentation at a participating center. However, the isolated assessment of TNF-α genotypes and plasma levels may be misleading without consideration of other interacting cytokines.

Although TNFA2 and TNFB2 have been correlated with increased TNF-α release by endotoxin-stimulated leukocytes, in vivo control of TNF-α synthesis is complex and downregulated by anti-inflammatory cytokines including interleukin (IL)-4 and IL-10. An autoregulatory loop appears to exist whereby TNF-α induces IL-10 production, which ultimately reduces TNF-α synthesis.2 Three functional polymorphisms have been described for the IL-10 promoter, with single base pair substitutions at positions −1082, −819, and −592.3 In particular, substitution of guanine for adenine at position −1082 has been correlated with low IL-10 production after T-cell stimulation.3 The potential clinical importance of this finding was highlighted by a recent study4 demonstrating a strong association between the combined low IL-10/high TNF-α (TNFA2) genotype and early graft rejection in a population of heart transplant recipients. Other recent studies5 have demonstrated the complementary importance of IL-10 and TNF-α in patients with bacterial sepsis and have indicated an increased mortality in patients with a high plasma IL-10 to TNF-α ratio. Selection pressures may therefore exist to ensure persistence of the high TNF-α/low IL-10 genotype because of potential resistance to bacterial infection. Further studies are warranted to assess whether this combined genotype predisposes toward the development of heart failure in an unselected population.

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Percutaneous Transluminal Coronary Angioplasty Reverses Vasoconstriction of Stenotic Coronary Arteries in Hypertensive Patients
To the Editor:
We read with interest the study by Frielingdorf et al1 in which exercise-induced dilation (measured by biplane angiography) of “normal” coronary arteries was impaired in hypertensive compared with normotensive patients. The vasodilator response in normal arteries during exercise is dependent on flow-sensitive release of nitric oxide from the endothelium.2 However, attributing an impaired dilator response in hypertensives to deficient release of endothelium-derived vasodilators (“endothelial dysfunction”) dismisses the alternative potential importance of variability in exercise-induced flow.

Demonstration of impaired flow-dependent dilation requires measurement of flow; however, few studies in this field measure and adjust for it. It is well known that microvascular disease reduces the hyperemic response to exercise. Indeed, coronary flow reserve has been shown to be significantly impaired in hypertensives, even in the absence of left ventricular hypertrophy, probably as a result of perivascular fibrosis, microvascular remodeling, and reduced diastolic perfusion time due to impaired ventricular relaxation.3,4 Thus, in hypertensive patients, reduced vasodilation during the coronary hyperemic response to exercise is likely to be due, at least in part, to a blunted increase in flow. Similarly, vasoconstrictor responses with exercise may be an appropriate response, because flow through stenotic segments may actually be reduced with exercise owing to partial perfusion of the distal bed by collaterals, or steal, which results from a greater relative drop in vascular resistance in neighboring vascular beds. In addition, circulating catecholamine levels5 and cardiac uptake of catecholamines6 are increased in hypertension and may attenuate both microvascular and macrovascular dilation.

Unfortunately, exactly how much dilation is expected for each increment in flow is unknown. It is therefore uncertain to what degree an attenuated vasodilator response is due to macrovascular and microvascular endothelial dysfunction, respectively. It would be interesting to know whether macrovascular endothelial dysfunction represents a shift of the curve to the right, a blunting of the slope of the flow/dilation curve, or a reduction in the maximal dilation response. Although these considerations are particularly pertinent to the coronary circulation in hypertensives, they may also affect interpretation of studies that measure flow-mediated dilation after forearm ischemia. Perhaps a more thorough exploration of these methodological issues would lead to consensus on exactly what values constitute abnormal macrovascular endothelial function.

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Insertion/Deletion Polymorphism of the Angiotensin-Converting Enzyme Gene and Hypertension

To the Editor:

Recently, an analysis was performed using a prospective, longitudinal, population-based sample in which the insertion/deletion (I/D) polymorphism of the ACE gene was postulated as a sex-specific candidate gene for hypertension. 1 A significant association between hypertension in males and the ACE DD genotype was observed after adjustment for all confounders (OR 1.59, \( P = 0.02 \)), whereas linkage between the DD genotype and diastolic blood pressure (DBP) in men was significant only when adjusted for age alone (\( P = 0.03 \) and \( P = 0.16 \) after and before adjustment for age, respectively).

In contrast, an independent prospective, population-based study found no association between the ACE I/D polymorphism and hypertension, nor was there any sex stratification with regard to allele or genotype. 2 Adjustment for several potential confounders did not affect this result for isolated systolic hypertension (systolic blood pressure [SBP] ≥ 160 mm Hg, DBP ≤ 90 mm Hg) (II versus DD OR 1.06; I versus D OR 1.09) or systolic-diastolic hypertension (SBP ≥ 160 mm Hg, DBP ≥ 90 mm Hg) (II versus DD OR 1.19; I versus D OR 1.16).

O’Donnell et al. 3 used the Framingham cohort, which has a large sample size (\( n = 3095/1044 \) sib pairs) and allowed use of both association analyses and pedigree-based linkage analyses, which provides considerable power to the study. The Dubbo cohort subset used by Johnson et al. 4 is smaller (\( n = 233 \)) but epidemiologically superior, with a sound geographical definition.

The most obvious differences between these studies are the definition of high blood pressure and the criteria used to classify patients. O’Donnell and coworkers 1 classified patients as having hypertension on the basis that they were using antihypertensive medication or that SBP was ≥ 140 mm Hg or DBP ≥ 90 mm Hg. Subjects administered antihypertensive medication were excluded altogether by Johnson et al. 4 to avoid misclassification and to minimize the introduction of serious flaws in the regression of genotype, whereas subjects with SBP ≥ 160 mm Hg would be classified as normotensive.

The mean age of the Framingham subjects studied was in the mid to late 50s, considerably younger than the Dubbo subset (late 60s). It remains a possibility that the Dubbo cohort signifies an older, progressive representation of the Framingham cohort that has suffered the removal (through premature death) of those subjects with a genetic predisposition to hypertension. The more stringent classification of high blood pressure in the Dubbo cohort, however, would tend to belie this possibility. Certainly, the concerns outlined above render any correlations between the ACE I/D variant and hypertension speculative at the present time.


Renin-Angiotensin System and Blood Pressure

To the Editor:

With great interest, we read the articles by O’Donnell et al. 1 and Fornage et al. 2 in the May 12, 1998, issue of Circulation. Their data suggest genetic linkage between the ACE gene and blood pressure in men but not in women. Likewise, we previously described associations of ACE with arterial blood pressure 3 and with ECG evidence of left ventricular hypertrophy 4 only in men. It may be worthwhile, therefore, to point to another apparent sexual dimorphism of the renin-angiotensin system. In men, renin and prorenin are ∼30% and 50% higher, respectively, than in women, 5 a difference that may diminish during menopause. Renin is the second major enzyme of this system and is responsible for generation of angiotensin I (the substrate of ACE). It may thus be speculated that men with genetically elevated ACE levels (DD genotype) are confronted with higher angiotensin I levels and, thereby, may have a higher chance to present with complex phenotypes. The stoichiometry of ACE and renin was also probed by a recent transgenic rat model with high levels of human ACE transgene expression in the heart. 6 Although this transgenic animal has almost no apparent phenotype under baseline conditions, abdominal aortic banding and subsequently high renin levels resulted in enhanced left ventricular hypertrophy. Similarly, Montgomery et al. 7 found a much more marked increase in left ventricular mass in response to intense physical training in males with the ACE D allele than in II homozygotes, whereas left ventricular mass was similar in the genotype groups before training.

Taken together, genetic polymorphisms should be placed in the context of the physiological system to which they relate. Given that these physiological systems may be subject to feedback or gender-specific regulation, interpretation of respective analyses should pay attention to these factors, as exemplified by O’Donnell, Fornage, and their coworkers.

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1. O’Donnell CJ, Lindpaintner K, Larson MG, Rao VS, Ordovas JM, Schaefer EJ, Myers RH, Levy D. Evidence for association and genetic linkage of the angiotensin-converting enzyme locus with hypertension...
Increased Membrane and Soluble P-Selectin in Atrial Fibrillation

To the Editor:

Inappropriate platelet activation and thrombus formation are frequent findings in many cardiovascular disorders and are believed to have an important pathogenic role. P-selectin, the membrane component of α-granule and membrane of the Weibel-Palade body, aids the adhesion of leukocytes bearing its ligand. Increased expression of P-selectin at the surface of the platelet, as defined by flow cytometry, is therefore a likely association of angiotsin-converting enzyme gene and artery vascular hypertrophy. N Engl J Med. 1994;330:1634–1638.

To investigate this further, we recruited 52 consecutive patients (45 males, mean age 66 years) with chronic AF who were not taking any antithrombotic therapy and 60 age- and sex-matched healthy controls. P-selectin was measured in citrated plasma by commercial ELISA (R&D Systems). Mean ± SD levels in the patients with AF were 232 ± 181 ng/mL compared with 161 ± 82 ng/mL in the controls (unpaired t test P = 0.015). Like Minamino and colleagues,2 we would interpret our preliminary data showing raised sP-selectin in AF as evidence of increased platelet activation in our patients.

Our findings may be applicable to other forms of atherothrombotic disorders, such as stroke, and warrant further attention in larger groups of patients with more diverse disease(s). If raised sP-selectin levels are truly a marker of platelet activation, this may possibly provide a new rationale for developing and using therapy targeting platelets. sP-selectin would also be an easily measurable index of platelet activation, allowing large-scale epidemiological and prognostic studies in AF and other disorders to be performed without encountering the limitations imposed by complex flow cytometry.

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**Response**

We thank Dr McKenna for his valuable comments on our study. In the study published in the November 3, 1998, issue of *Circulation*, we determined the absence of a family history of patients with dilated cardiomyopathy (DCM) by use of a detailed questionnaire. We have confirmed that there were no relatives diagnosed with DCM, heart failure, or severe arrhythmia or who experienced documented sudden death. However, we have not performed echocardiographic screening in patients’ relatives. Although accurate data for the frequency of familial prevalence are currently not available in Japan, familial DCM is relatively rare, especially in middle-aged individuals (mean age of our DCM subjects was 55.8 ± 12.4 years). Therefore, we believe that our DCM subjects were sporadic cases. We agree with Dr McKenna that echocardiographic screening of patients’ relatives is important and useful for detection of familial prevalence. Recently, Olson et al identified missense mutations in the cardiac actin gene as a genetic determinant of familial DCM. In the near future, we will need to screen gene mutations to determine whether DCM is familial.

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Increased Membrane and Soluble P-Selectin in Atrial Fibrillation
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