Tumor Necrosis Factor-α and Interleukin-10 Genotypes in Congestive Heart Failure

To the Editor:

The allelic case-control study by Kubota et al. 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 leukocyes, 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. Two functional polymorphisms have been described for the IL-10 promoter, with single base pair substitutions at positions −1082, −819, and −592. In particular, substitution of guanine for adenine at position −1082 has been correlated with low IL-10 production after T-cell stimulation. The potential clinical importance of this finding was highlighted by a recent study 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 studies 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 unscreened 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 al. 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. 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. 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 levels and cardiac uptake of catecholamines 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, 5% $P$=0.03 and 5% $P$=0.16 after and before adjustment for age alone, 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] $\geq$160 mm Hg, DBP $\geq$90 mm Hg) (II versus DD OR 1.06; I versus D OR 1.09) or systolic-diastolic hypertension (SBP $\geq$160 mm Hg, DBP $\geq$90 mm Hg) (II versus DD OR 1.19; I versus D OR 1.16).

O’Donnell et al3 used the Framingham cohort, which has a large sample size (n=2095/1044 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 al2 is smaller (n=33) but epidemiologically superior, with a sound geographical definition.4 The most obvious differences between these studies are the definition of high blood pressure and the criteria used to classify patients. O’Donnell and coworkers3 classified patients as having hypertension on the basis that they were using antihypertensive medication or that SBP was $\geq$140 mm Hg or DBP $\geq$90 mm Hg. Subjects administered antihypertensive medication were excluded altogether by Johnson et al2 to avoid misclassification and to minimize the introduction of serious flaws in the regression of genotype, whereas subjects with SBP $\leq$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.


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 of the 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 marker of the activation of these cells.1

The recent article by Minamino and colleagues2 reporting increased expression of P-selectin by platelets in subjects with atrial fibrillation (AF) is therefore in keeping with platelet activation and a prothrombotic state in AF, leading to the high risk of stroke and thromboembolism in this common condition. Nevertheless, a soluble form of P-selectin (sP-selectin) is also present in the plasma, and increasing evidence points toward elevated plasma levels among patients with thrombotic disorders, stroke, and atherosclerosis, thus providing an additional tool to study platelet activation.3,4 Similar to Minamino and colleagues,2 we hypothesised that patients with AF would have raised levels of sP-selectin.

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. sP-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 Blann and his colleagues for the important comments on the results presented in our recent publication in Circulation.1 Our experimental and clinical data revealed that the increased expression of P-selectin on platelets with reduced nitric oxide levels was a risk factor for silent cerebral infarction in patients with atrial fibrillation (AF). Dr Blann further provided interesting data that plasma levels of soluble P-selectin in patients with AF were higher than those in age- and sex-matched controls, which seems to be consistent with our observation. However, since P-selectin is expressed in endothelial cells as well as platelets,2 plasma soluble P-selectin is believed to be liberated from endothelial cells as well as platelets in the pathophysiological condition.3 Therefore, the higher plasma levels of soluble P-selectin in patients with AF may be attributable to endothelial damage as well as to platelet activation in those patients. We have experimentally observed a reduction in plasma levels of nitrate and nitrate (stable end products of nitric oxide) after the onset of AF, which suggests the possibility that an irregular change in the shear stress of the cardiovascular system may impair endothelial function.4 Indeed, Lip and colleagues5 reported that von Willebrand Factor (vWF), an established marker of endothelial dysfunction, is increased in patients with AF, which suggests that endothelial damage may occur in those patients. vWF is known to colocalize with P-selectin in the Weibel-Palade bodies of endothelial cells and to mobilize with P-selectin after certain stimuli. Thus, it is likely that the elevation of plasma soluble P-selectin levels may reflect both endothelial dysfunction and platelet activation in patients with AF. Since both endothelial dysfunction and platelet activation may be involved in thrombus formation in patients with AF, we agree that the measurement of plasma soluble P-selectin is promising as an integrated marker of endothelial dysfunction and platelet activation in patients with AF. It is intriguing to investigate the kinetics of soluble P-selectin in patients with AF for the prediction of cerebral infarction.

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To the Editor:

Familial Dilated Cardiomyopathy

To the Editor:

The article by Ichihara and colleagues published in the November 3, 1998, issue of Circulation describes an association between a G→T missense mutation in the plasma platelet-activating factor acetylhydrolase gene and genetic susceptibility to nonfamilial dilated cardiomyopathy (DCM).1 No definition of familial DCM was excluded in the study and whether any 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 al2 identified missense mutations in the cardiac actin gene as genetic determinants of familial DCM.3 In the near future, we will need to screen gene mutations to determine whether DCM is familial.

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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 al2 identified missense mutations in the cardiac actin gene as a genetic determinant of familial DCM. There are several more chromosomal loci responsible for familial DCM.3 In the near future, we will need to screen gene mutations to determine whether DCM is familial.

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