Factor V Leiden, Prothrombin 20210 Gene Variant, and Risk of Myocardial Infarction

To The Editor:

Doggen et al. reported a case-control study assessing the effect of factor V Leiden and the prothrombin 20210 gene variant on the risk of myocardial infarction in men. The authors stated in their conclusions that “the 20210 G→A variant of prothrombin is associated with an increased risk of myocardial infarction” and that “the combined presence of major cardiovascular risk factors and carrying of a coagulation defect increases the risk considerably.”

A review of their data in Tables 1 through 4 leads us to conclude that neither claim is supported by statistical significance. In Table 2, the prevalence of the prothrombin variant in cases (1.8%) is not significantly different from the prevalence in controls (1.2%). In Table 3, the prevalence of factor V Leiden, shown in Table 3, appears possibly to have overlap of the CIs suggests that a significant difference between the 1.2% in the general population(2%) rather than a higher prevalence in the cases.

The second conclusion, that a coagulation defect added to the effect of a metabolic defect, also does not stand up to scrutiny of the data. In Table 3, the ORs of 6.1 and 3.3, with their overlapping CIs of 3.0–12.5 and 2.5–4.2, respectively, indicate that smoking increased the risk of myocardial infarction, with or without a coagulation defect, but do not prove that factor V Leiden or the prothrombin variant significantly added to the risk. Without access to the original data, we cannot calculate the P value for this comparison of age-adjusted ORs, but the wide overlap of the CIs suggests that a significant difference between the 2 ORs was not found. Similar observations apply to the subset analyses of the effect of obesity and hypertension in Table 4. Only the pooled data for any “metabolic defect” and any coagulation defect, shown in Table 3, appear possibly to have achieved statistical significance. The authors should have explicitly stated the presence or absence of statistical significance for each of the comparisons of risk that they published in Tables 1 through 4, a minimum of 23 comparisons, for which a P value of <0.05 may be found at least once by chance. We conclude that the authors have not proven that the prothrombin 20210 gene variant, in the absence of factor V Leiden, increases the risk of myocardial infarction.

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MRI for the Diagnosis and Follow-Up of Myocarditis
To the Editor:

We read with interest the elegant study by Friedrich and associates1 about the usefulness of MRI in the evaluation of myocardial changes in acute myocarditis. The authors evaluated the variation in T1-weighted sequences with gadolinium enhancement over time in 19 patients with clinically suspected myocarditis. In 7 patients, an endomyocardial biopsy (EMB) was also performed, and the morphological pattern was compared with the MRI acquirments to assess correlation between the 2 diagnostic tools. They conclude that contrast-enhanced, T1-weighted sequences performed during the first 2 weeks after the onset of symptoms elucidate the evolution of the inflammatory process from a focal to a diffuse myocardial disease. They also state that T2-weighted sequences yield a poorer-quality image, with signal intensity not being statistically different from controls.

In contrast, it has been our experience2 that MRI T2-weighted sequences are able to discern patients with or without myocarditis. We are currently performing a study on 75 consecutive pediatric patients with symptoms of acute congestive heart failure, left ventricular enlargement with depressed systolic function, and no evidence of congenital heart disease. All children were submitted to both EMB and MRI. The invasive study identified 51 patients with acute myocarditis and 24 dilative cardiomyopathies. Compared with the gold-standard EMB, our MRI images, based on T2-weighted sequences, achieved a sensitivity of 100% and a specificity of 90% (Gagliardi, unpublished data, 1998). It must be noted that 2 patients with negative EMB but positive MRI were actually affected by myocarditis, which was later correctly diagnosed on the basis of their clinical outcome. An EMB sampling error was probably the cause of these 2 “false false-positives” at MRI, reinforcing the opinion of a higher diagnostic accuracy of MRI with respect to EMB in the early, focal phase of myocarditis.1

The resulting 53 children affected by myocarditis have been submitted to repeated EMB and MRI every 6 months to evaluate the efficacy of MRI in identifying persistent, resolving, or resolved myocarditis during a 2-year follow-up period. Our preliminary data3 confirm the usefulness of MRI evaluation of signal intensity increase with T2-weighted sequences during follow-up, because its sensibility and specificity remain high throughout the entire evolution of the disease. It is also interesting to note that during follow-up, the results of EMB do not take into account the reduction of the extension of the inflammatory process on the entire ventricle. Conversely, MRI (recording signals from the entire ventricle, both right and left) provides more precise information about the presence and the extension of the inflammatory process. This approach is particularly useful when the evolution of signal intensity variation is being evaluated in the single patient over time.

We conclude with Friedrich et al1 that the use of MRI during the early phase and the follow-up of myocarditis provides highly reliable clinical information while decreasing risk and discomfort related to invasive procedures.

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Response

We are grateful to Gagliardi and coworkers for their valuable comment on our study. They correctly stress the important role of T2-weighted MRI in patients with acute myocarditis. Because heavy T2 weighting leads to an almost exclusive signal of water-bound protons, myocardial edema should be easily visualized by this technique. As we pointed out in our article, because of the impaired quality of the conventional T2-weighted images, we were not able to detect a significant difference in patients compared with controls. However, in the same article, we report preliminary results in 6 patients with significant changes in T2-weighted breath-held images.1 We have since continued this study using a heavily T2-weighted breath-holding MR sequence (STIR, or Short T1 Inversion Recovery) in the same scanner (Siemens Magnetom Expert 1.0 T). The skeletal muscle was used as an internal reference, and a ratio of global myocardial to skeletal muscular signal was calculated. In contrast to 13 volunteers, there were areas of a strong myocardial signal in all 11 patients during the follow-up of acute myocarditis. The ratio of global myocardial to skeletal muscular signal was significantly higher on days 7, 14, 28, and 84 after the onset of symptoms but not on day 2. Because this technique is a “water image,” the stronger signal observed in patients most likely represents edema due to inflammation. Thus, visualization of edema seems to be a reasonable approach in visualizing acute myocarditis. However, this phenomenon was not present very early after the onset of the disease. Furthermore, myocardial damage may persist after the edematous phase, and the disease activity may be missed by just T2-weighted MRI. We are currently evaluating the use of both breath-held T2, for visualizing edema, and contrast-enhanced T1 to detect edema and cellular damage. Both techniques may give additive information on the disease process. Our initial data suggest that this approach is a fast and reliable noninvasive technique to establish or exclude acute or subacute myocarditis. We encourage Gagliardi and colleagues to continue their important work.

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Homocysteine, B Vitamins, and Atherosclerosis

To the Editor:

The conclusion by Folsom et al,\(^1\) that raised homocysteine concentrations in the blood may be a consequence, not a cause, of coronary artery disease has serious clinical implications. As McCully\(^2\) pointed out in his recent editorial, arteriosclerosis in coronary artery disease has serious clinical implications. As concentrations in the blood may be a consequence, not a cause, cysteinemia also leads to atherogenesis.\(^2\)

Rimm et al\(^2\) observed an independent inverse association between vitamin B\(_6\) (serum pyridoxal 5\(^\prime\)-phosphate) and CHD incidence. Although our results for tHcy were null, we agree with Dr Cheng that tHcy could still prove to be important in CHD. We also believe there are few reasons not to fortify cereals and advocate that everyone eat diets that could provide the recommended daily allowances for folate and vitamins B\(_6\) and B\(_{12}\). However, we disagree with Dr Cheng’s view that clinicians should “not wait for the results of the randomized trials” if he means widespread screening for elevated tHcy and aggressive prescription of vitamin supplements.

Epidemiological and clinical observations occasionally lead to incorrect conclusions about causality of complex diseases like CHD. Take as examples recent experience with beta-carotene and estrogen and medroxyprogesterone acetate replacement, for which there was considerable epidemiological evidence to suggest both may prevent CHD events, but clinical trials proved to be ineffective.\(^1,4\) Randomized clinical trials eliminate confounding (eg, other lifestyle characteristics incompletely accounted for in statistical analysis, such as diet or access to and attitudes regarding health care) and provide a truer picture of cause and effect than observational studies.

The basic and observational epidemiological data on tHcy, B\(_6\), and folate, though intriguing, do not prove a causal role of tHcy for the majority of patients who develop CHD. We believe that until there are clinical trial data supporting tHcy lowering, screening for elevated tHcy and widespread prescription of folate and vitamins B\(_6\) and B\(_{12}\) are not warranted. Clinicians could consider measuring tHcy in selected high-risk patients, ie, those with atherosclerotic diseases or a strong family history, and prescribing vitamin supplementation if tHcy is elevated, because tHcy may be more prognostic in high-risk patients.\(^5\) Such a treatment is not supported by clinical trials, and this arbitrary decision should clearly accompany the simultaneous treatment of other traditional risk factors, like LDL lowering, hypertension control, and smoking cessation.

Response

Despite much evidence implicating homocysteine in atherosclerosis, ours is one of several prospective studies reporting no association between total homocysteine (tHcy) and coronary heart disease (CHD) incidence.\(^1\) We, like Rimm et al,\(^2\) observed an independent inverse association between vitamin B\(_6\) and CHD incidence. Although our results for tHcy were null, we agree with Dr Cheng that tHcy could still prove to be important in CHD. We also believe there are few reasons not to fortify cereals and advocate that everyone eat diets that could provide the recommended daily allowances for folate and vitamins B\(_6\) and B\(_{12}\). However, we disagree with Dr Cheng’s view that clinicians should “not wait for the results of the randomized trials” if he means widespread screening for elevated tHcy and aggressive prescription of vitamin supplements.


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