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 carriehship 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%) by the χ² test, with an OR of 1.5 and a CI (0.6–3.8) that includes unity. A larger study would be required to prove that an OR of 1.5 is truly increased. The likelihood that this OR of 1.5 is not significantly different from 1.0 is also suggested by the fact that it is based on the unexpected finding of a lower prevalence of the variant in the controls (1.2%) than 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 applications 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.

Mae B. Hultin, MD
Professor of Medicine and Pathology

Response

The results of the “Study of Myocardial Infarctions Leiden” showed that the variant in the prothrombin gene (20210 G→A) increased the risk of myocardial infarction by 50% (OR, 1.5; 95% CI, 0.6–3.8). A similar effect was found for another prothrombotic defect, factor V Leiden, which increased the risk by 40% (OR, 1.4; 95% CI, 0.8–2.2). The effect was higher in those individuals with additional risk factors (ie, smoking, obesity, diabetes, hypertension, or hypercholesterolemia).

Hultin and Grimson question our conclusions because of concerns about statistical significance. We agree with their observations about the absence of statistical significance. We also believe this is largely irrelevant. Contrary to what Hultin and Grimson state, we do not think it possible to prove anything, nor do we attempt to do so. Single studies should not swing opinions, whether their results are significant or not. Our first aim is to estimate effects, ie, relative or absolute risks. In this case, our best estimate for the risk of myocardial infarction for carriers of the 20210 variant of the prothrombin gene is a 50% risk increase. Indeed, the 95% CI, which might be seen as a range of plausible values for this OR of 1.5, is 0.6 to 3.8, ie, does not exclude even a small protective effect, or a nearly fourfold increased risk. The most plausible effect, however, is the observed risk of 1.5 (maximum likelihood estimator). The consistently increased risk of myocardial infarction or coronary heart disease in the presence of the prothrombin variant in other studies lends further support to this estimate.

Hultin and Grimson may have missed the point about interaction: for each of the major cardiovascular risk factors, a coagulation defect had a higher relative risk in the presence than in the absence of that risk factor. For instance, for nonhypertensives, carriehship of a coagulation defect only increased the risk 1.2-fold; for hypertensives, this was 3.3-fold (similarly so for smokers, obese individuals, diabetics, and hypercholesterolemics). It is striking that this was the case for all these major risk factors, and this may be of public health importance because in these individuals, the risk of the genetic clotting defect is superimposed on a risk already elevated by classic cardiovascular risk factors. Again, our findings concerning interaction are consistent with the results of a previous study among young women. Consistency between studies is, in our view, more important than statistical significance: we try to elucidate a biological problem by clinical, epidemiological, and biochemical means. For this aim, the results of additional studies will be helpful.

Carine J.M. Doggen, MSc
Frits R. Rosendaal, MD, Professor
Volker Manger Cats, MD
Rogier M. Bertina, PhD
Department of Clinical Epidemiology
Department of Cardiology
Hemostasis and Thrombosis Research Center
Leiden University Hospital
Leiden, Netherlands


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 acquisitions 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 being not 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 sensitivity 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 al2 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.

M. Giulia Gagliardi, MD, PhD
Bruno Polletta, MD
Department of Cardiology and Cardiac Surgery
Bambino Gesa Children Hospital
Rome, Italy

Paolo Di Renzi, MD
Department of Radiology
Fatebenefratelli-Isola Tiberina Hospital
Rome, Italy

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.

Matthias G. Friedrich, MD
Oliver Strohm, MD
Jeanette Schulz-Menger, MD
Friedrich C. Luft, MD
Rainer Dietz, MD
Franz-Volhard-Klinik, Charité
 Humboldt Universität Berlin
Berlin, Germany
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 McCully2 pointed out in his recent editorial, arteriosclerosis in concentrations in the blood may be a consequence, not a cause, of hyperhomocysteinemia also leads to atherogenesis.2 The last enzymatic abnormality explains the origin of arteriosclerosis observed in vitamin B6-deficient monkeys and choline-deficient rats, 2 important animal models in which hyperhomocysteinemia may result from 3 different enzymatic defects: deficiency of cystathionine synthase, which is a pyridoxal phosphate–dependent enzyme; deficiency of methyltetrahydrofolate homocysteine methyl transferase, which is a cobalamin-dependent enzyme; and deficiency of methylene tetrahydrofolate reductase, which is a folate-dependent enzyme. The last enzymatic abnormality explains the origin of arteriosclerosis in vitamin B6-deficient monkeys and choline-deficient rats, 2 important animal models in which hyperhomocysteinemia also leads to atherogenesis.2

Although I agree with Folsom et al.1 that randomized trials are needed to better clarify the interrelationships of homocysteine, B vitamins, and atherosclerosis, the findings of a significant inverse relation between dietary intake of folate and vitamin B6, and mortality and morbidity from cardiovascular disease during a 14-year period in the Nurses’ Health Study, recently reported by Rimm et al.3 encourage the view that, with intervention through fortification, improved dietary intake of folate and vitamin B6, and food processing and distribution methods, the decline in US cardiovascular mortality and morbidity will continue.2

As my mentor, the late Dr Paul D. White, taught me, atherosclerosis begins in early childhood. Therefore, the simplest dietary precautions, adopted early in life, can substantially lower the risk of coronary artery disease.4 After being ignored for many years since the publication of the original animal work of McCully and Wilson,5 homocysteine has finally reemerged as a risk factor for the development of human atherosclerosis.6 Let us not wait for the results of the randomized trials, some of which are under way, suggested by Folsom et al.1 before we take decisive actions in the modern-day management of patients with coronary artery disease.

Tsung O. Cheng, MD
Professor of Medicine
The George Washington University
Washington, DC

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 B6 (serum pyridoxal 5’-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 B6 and B12. 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.3,4 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, B6, 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 B6 and B12 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.

Aaron R. Folsom, MD
Paul G. McGovern, PhD
Division of Epidemiology
School of Public Health
Michael Y. Tsai, PhD
John H. Eckfeldt, MD, PhD
Department of Laboratory Medicine and Pathology
University of Minnesota
Minneapolis, Minn

F. Javier Nieto, MD, PhD
Department of Epidemiology
School of Hygiene and Public Health
Johns Hopkins University
Baltimore, Md

M. René Malinow, MD
David L. Hess, PhD
Laboratory of Cardiovascular Diseases
Oregon Regional Primate Research Center
Beaverton, Ore

C.E. Davis, PhD
Collaborative Studies Coordinating Center
Chapel Hill, NC

References


MRI for the Diagnosis and Follow-Up of Myocarditis
M. Giulia Gagliardi, Bruno Polletta and Paolo Di Renzi

Circulation. 1999;99:457a-460
doi: 10.1161/01.CIR.99.3.457.a

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/99/3/457a

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/