Body Iron Stores, Infection, and Risk of Acute Myocardial Infarction

To the Editor:

Tuomainen et al have noted an association between increased iron stores, as measured by a reduced ratio of serum transferrin receptor concentration to serum ferritin concentration, and excess risk of acute myocardial infarction (AMI).

It has been suggested that iron can catalyze toxic redox reactions, which may lead to an increased risk for coronary heart disease and AMI. Another mechanism by which iron might increase the risk of AMI involves a possible role for iron in facilitating some infections.

Vertebreates have a hypoferremic response during infection that lowers the presence of iron as serum transferrin, temporarily storing the metal as ferritin. Intestinal absorption of iron also declines during infection. Bacterial mechanisms to obtain iron from a host include direct uptake of iron from the labile iron pool, siderophore-mediated iron uptake, and iron uptake by direct interaction with transferrin, lactoferrin, or heme-containing proteins.

Various mechanisms by which infectious processes might induce atherogenesis have been proposed, including cytotoxic effects of infection on endothelial and smooth muscle cells, formation of circulating toxins or immune complexes that deposit on vessel walls, elicitation of an inflammatory response, induction of alterations of serum prostaglandin and lipid metabolism, or elicitation of a hypercoagulable state that increases the risk of thrombosis.

Recent research has suggested that numerous organisms may be associated with an increased risk of AMI. These include Helicobacter pylori, Chlamydia pneumoniae, herpes simplex virus, and cytomegalovirus.

Several investigators have noted the importance of iron acquisition for H pylori growth. No studies have reported on the iron requirements of C pneumoniae. However, Raulston noted that iron restriction caused a significant reduction in infectivity of C trachomatis elementary bodies. The smaller subunit (R2) of herpes simplex virus ribonucleotide reductase, which catalyzes the reduction of ribonucleotides to deoxyribonucleotides, contains binuclear ferric iron centers; ferrous iron is necessary to generate the binuclear ferric iron centers and to ensure full enzymatic activity. Gumbel et al noted that desferrioxamine, an iron chelator with antitherpetic activity, can inhibit cytomegalovirus infection in vitro and in vivo. It had been proposed that 1 mechanism of action by which desferrioxamine and other iron chelators inhibit various infections might involve ribonucleotide reductase inhibition.

Further studies are needed to investigate the possible role of infections in the etiology of AMI and of iron in promoting those infections.

Michael Rabinoff DO, PhD
UCLA Neuropsychiatric Institute and Hospital
Los Angeles, Calif

Response

We thank Dr Rabinoff for his interesting comments on our study of body iron and the risk of first acute myocardial infarction. We agree that iron is an essential nutrient and enzyme cofactor in different infectious agents as well as in humans. The role of some infectious agents, especially of Helicobacter pylori, Chlamydia pneumoniae, herpes simplex virus, and cytomegalovirus, in the etiology of cardiovascular disease has been studied by several study groups, but no solid conclusions can yet be drawn. Most of the studies that support this association have been small, and positive publication bias seems very likely. Although we acknowledge that high body iron may predispose to some potentially cardiovascular disease–related infections, we would emphasize the inflammation itself. Plenty of evidence links inflammation and both central and peripheral atherosclerosis.

If atherosclerosis is taken as a chronic inflammatory disease, it is likely that any factor that enhances inflammation accelerates the process of atherogenesis.

However, the direct effect of elevated body iron in driving different free radical–generating reactions that propagate lipid peroxidation and cause untargeted direct and indirect oxidative damage in arterial wall and in myocytes is probably far more important. Whether high iron predisposes to coronary heart disease or low iron protects against it remains to be ascertained. Currently, high (elevated) body iron appears to be a risk-increasing factor in cardiovascular disease, independent of infections.

Tomi-Pekka Tuomainen, MD
Kristiina Nyysönén, PhD
Jukka T. Salonen, MD, PhD
Research Institute of Public Health
University of Kuopio
Kuopio, Finland
Kari Punnonen, MD, PhD
Department of Clinical Chemistry
Kuopio University Hospital
Kuopio, Finland


Long-Term Therapy for Postmenopausal Osteoporosis: Stronger Bones but Weaker Arteries?

To the Editor:

The intriguing article by Jono et al suggests that long-term supplementation with vitamin D for postmenopausal osteoporosis may increase vascular calcification. This is not a new concept and raises important and practical issues.

Alendronate, an inhibitor of osteoclast-mediated bone resorption, is widely promoted for the treatment and prevention of osteoporosis in postmenopausal women. This group of women

446

Downloaded from http://circ.ahajournals.org/ by guest on April 19, 2017
is at higher risk for cardiovascular disease. Vascular calcification has many similarities to that of bone, and vascular wall macrophages may have both osteoblastic and osteoclastic potential.

Calcification alters the mechanical properties of the atherosclerotic plaque. It may lead to increased stress near the shoulder of the plaque, leading to rupture. On the other hand, extensive calcification and fibrosis may stabilize plaque.

Therefore, in addition to vitamin D supplementation, long-term therapy for postmenopausal osteoporosis with alendronate may lead to plaque instability and increased cardiovascular events in a population already at increased risk. Diligent postmarketing surveillance of this drug is necessary to monitor these issues.

It would be unfortunate to make bones stronger at the expense of making arteries weaker.

Mark R. Goldstein, MD
Crozer-Keystone Health Network
Springfield, Pa


Indirect Individual Circadian Variation and Sudden Death

To the Editor:

Because the identification of patients with certain circadian trends may permit individualized prevention of cardiac arrest or sudden death, we read the article by Peckova et al with interest. We were, however, puzzled by the investigators’ results emphasizing that the phenomenon of individual circadian variation for sudden cardiac death was not present. We believe there are important caveats to heed when one interprets these results.

In 1995, when analyzing the distribution of sudden death due to ventricular fibrillation (VF) aborted by implanted defibrillators (ICDs), we reported a clear tendency for shocks to occur in the morning hours in a group of 22 patients. Interestingly, 16 patients who received multiple appropriate shocks showed a trend for the repeated shocks to occur around the same period of the day that the initial shock occurred. Two patients each experienced 6 shocks that occurred within the same 3-hour period of the day. This trend was noted even when subsequent shocks occurred as long as 1 year after the initial shock. Such findings strongly suggested that an individual circadian variance in sudden death due to VF could exist in patient subgroups.

Our results, however, were limited by our small study group. Peckova et al have offered us a large cohort of patients with their analysis of temporal variation in 6603 out-of-hospital cardiac arrests and suggested that women formed the sole group to demonstrate any significant similarity in the time of day the first and second arrests occurred. However, some characteristics in Peckova’s study group might have concealed individual circadian variance.

Namely, Peckova’s data consider all arrhythmias, regardless of the type. Therefore, it is not clear whether patients with recurrent cardiac arrest had the same type of arrhythmic event during the first and subsequent episodes. Different arrhythmic events have different circadian variations. We believe this fact necessitates that analysis should contemplate only patients in whom the cause is the same for the first and subsequent arrests. Additionally, the authors included data acquired by rescue services. Generally, patients without an ICD experience a limited number of cardiac arrests. Data obtained from the ICD are
incomparably more precise than data acquired by rescue services. Therefore, data obtained from ICDs are the best way to identify individual circadian rhythms for arrhythmic sudden death.

Because of these limitations, we believe the issue of individual circadian variance for arrhythmic death still begs for further analysis and continued discussion.

André d’Avila, MD
Heart Institute (InCor)
University of São Paulo Medical School
São Paulo, Brazil

Pedro Brugada, MD
Professor of Cardiology
Cardiovascular Research and Teaching Institute
OLV Hospital
Aalst, Belgium

Response

The letter from Drs Avila and Brugada is interesting, and we certainly agree with their conclusion that the issue of individual circadian variance for arrhythmic death begs for further analysis and continued discussion. For the patients we studied with recurrent cardiac arrest, the rhythm when the emergency medical services team dispatched for the first cardiac arrest arrived was ventricular fibrillation. As such, we cannot know with certainty what the initial rhythm was for the tachycardia degenerating to ventricular fibrillation. However, we do agree with their conclusion that the issue of individual circadian rhythms for arrhythmic sudden death. Therefore, data obtained from ICDs are the best way to identify incomparably more precise than data acquired by rescue services.


Clinical Expression in Patients With Hypertrophic Cardiomyopathy Caused by Cardiac Myosin-Binding Protein C Gene Mutation

To the Editor:

Hypertrophic cardiomyopathy is a primary cardiac disorder, mostly genetically transmitted, with a heterogeneous clinical and morphological expression. Analysis of the clinical expression of several genetic alterations has previously focused mainly on unfavorable manifestations. In this regard, recent articles by Charron and colleagues and by Niimura and colleagues that describe delayed expression of cardiac hypertrophy and a favorable clinical course in patients with mutations in the gene for cardiac myosin-binding protein C (MyBP-C) are indeed important contributions to an understanding of phenotype-genotype correlations at the mild end of the spectrum of the disease. However, these reports did not include precise morphological distribution of left ventricular hypertrophy, which is of clinical importance in the diagnosis and management of patients with this disorder.

We had opportunities to study 6 probands from 6 small Japanese families living in Kochi prefecture who were found to have the same mutation in the cardiac MyBP-C gene: a 1-base deletion at codon 593 from TCC (Ser) to CC in exon 18. Of 30 adult family members screened, 14 were identified as having this MyBP-C mutation. Although disease penetrance was incomplete, 90% of all patients and 80% of those under the age of 50 years had cardiac hypertrophy. The mean maximal wall thickness was 21 ± 3 mm. Most patients revealed hypertrophy of both the ventricular septum and the free wall: 14 with Maron type III, 1 with type I, 1 with type IV, and 2 with diffuse concentric hypertrophy. There was no patient with apical hypertrophy, which was characteristically reported among Japanese patients. It would be interesting and clinically valuable to know what kind of morphological patterns of left ventricular hypertrophy, assessed by 2-dimensional echocardiography, have been seen in the patients reported by Charron and colleagues.

Concerning the natural history, sudden cardiac death was not observed during a follow-up period of 54.5 ± 57.1 months (range, 1 to 160 months) in our patients, and 3 patients reached the age of ≥ 70 years. However, it is worth noting that 4 patients gradually progressed to the stage of left ventricular dilation and dysfunction later in their lives, a fact that has not been reported previously.

This phenotype-genotype information will be of significant importance for the practicing clinician, because left ventricular hypertrophy, as well as left ventricular dilation and dysfunction, often occurs in elderly patients, particularly in association with systolic hypertension.

Yoshinori L. Doi, MD
Hiroaki Kitaoka, MD
Nobuhiko Hitomi, MD
Department of Medicine and Geriatrics
Kochi Medical School
Kochi, Japan

Manatsu Satoh, MD
Akiko Kimura, MD
Medical Research Institute
Tokyo Medical and Dental University
Tokyo, Japan
logical distribution of LVH was therefore variable in families related to the MyBP-C gene, even within a given family.

**Correspondence**

Philippe Charron, MD
Mohammed Bennaceur, MD
Richard Isnard, MD
Michel Komajda, MD

Service de Cardiologie

Lucie Carrier, PhD
Gisele Bonne, PhD
Ketty Schwartz, PhD

INSERM Unit 153

Anne-Claude Camproux, PhD
GERC, Département de Biomathématiques

Pascale Richard, PhD
Bernard Hainque, PhD
Service de Biochimie
Hôpital Pitié-Salpêtrière

Olivier Dubourg, MD
Service de Cardiologie
Hôpital Ambroise Paré
Boulogne, France

Michel Desnos, MD
Albert Hagege, MD
Service de Cardiologie
Hôpital Boucicaut
Paris, France

Jean Marc Langlard, MD
Jean-Brieuc Bouhour, MD
Service de Cardiologie
Hôpital Laennec
Nantes, France

---


**Response**

We thank Dr Doi et al for their comments about our article on phenotype-genotype analysis related to the cardiac myosin-binding protein C (MyBP-C) gene in familial hypertrophic cardiomyopathy (FHC). They screened Japanese families, found a mutation in the MyBP-C gene in 6 of them (14 adult members), and analyzed some of their clinical features. They found that penetrance of the disease was incomplete, as in our experience, but was as high as 80% before 50 years of age. First, the penetrance of the disease depends heavily on the diagnostic criteria used, as was recently shown in children.2 Therefore, it would be interesting to know the diagnostic criteria used by Doi et al. Second, in addition to the causative mutation or gene, many factors could modulate the expression of the disease and could explain the difference observed between the Japanese and French populations. These factors include mean age, sex ratio, modifier gene (such as the ACE I/D polymorphism),3 and unknown environmental factors. Interestingly, a mean follow-up of 34 months was available in families studied by Doi et al, and no sudden cardiac death was observed. This confirms the good prognosis observed in our study in young subjects.1 The fact that 4 patients progressed to left ventricular dilation and dysfunction is also in accordance with our findings, because we observed 4 cardiac deaths or transplantations related to congestive heart failure (mean age, 65 ± 9 years) in our population. This evolution appears not specific of families with a mutation in the MyBP-C gene, because it was described in families with a mutation in the β-myosin heavy chain gene.1

Finally, the distribution of left ventricular hypertrophy (LVH) was not described in our study (it was not our purpose, because the distribution of LVH appears to be of little interest for prognostic implications). However, in 46 subjects with LVH, of the 76 carriers of a mutation in the MyBP-C gene, we found 2 (4.3%) subjects with Maron type I hypertrophy, 19 (41.3%) with type II, 24 (52.2%) with type III, and 1 with type IV (2.2%). As previously shown in FHC related to other genes,4 the morpho-
Clinical Expression in Patients With Hypertrophic Cardiomyopathy Caused by Cardiac Myosin-Binding Protein C Gene Mutation
Yoshinori L. Doi, Hiroaki Kitaoka, Nobuhiko Hitomi, Manatsu Satoh and Akinori Kimura

Circulation. 1999;100:446-449
doi: 10.1161/01.CIR.100.4.446.-c

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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/100/4/446.4

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/