

214 706 1173  
Fax 214 369 3685 or 214 706 1551

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Contact: John Weeks or Ann M. Williams  
(404) 222-5310

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## Round 2: autopsy study appears to refute link of excess iron to heart disease risk

ATLANTA, Nov. 11 -- When Finnish researchers suggested in 1992 that excess iron in the body increases risk for coronary heart disease, their finding made headlines around the world.

The report also prompted two Maryland researchers to turn to a unique resource -- a registry of more than 48,000 autopsies performed at Baltimore's Johns Hopkins Hospital between 1889 and 1993.

From the 48,000 autopsies the scientists studied 130 patients, comparing 65 adults whose records mentioned iron overload with another group of 65 "controls" carefully matched for age, race, sex and time of death. Of the 65 adults with iron overload, 32 more recent (since 1968) cases included examinations of the coronary arteries using "post-mortem coronary arteriography."

Analysis of the autopsy records shows "people with iron overload states do not appear to have significant amounts of coronary artery disease," concludes Michael Miller, M.D., director of preventive cardiology at the University of Maryland Medical Center, Baltimore. He and Grover M. Hutchins, M.D., professor of pathology and director of autopsy services at the Johns Hopkins Hospital, presented their findings here today at the American Heart Association's 66th Scientific Sessions.

"We decided to do the study because so much attention and excitement was focused on the question of whether iron is a risk factor for heart disease," Miller says. "Our hypothesis was if iron is an important risk factor, we would find coronary heart disease when we look at the most severe cases of iron overload."

Instead, they found a "surprising" lack of blocked coronaries among the iron overload cases. "We thought it was fascinating that only three of 65 hemochromatosis [iron overload] patients, or less than five percent, had one coronary artery with 90 percent or more blockage,"

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Miller says. "By contrast, three times as many controls -- 11 of 65, or 17 percent -- had significant coronary blockages."

Hemochromatosis is a metabolic disease marked by excess iron accumulation in body tissues, causing damage that can lead to major organ dysfunction.

Using a system of grades in which zero represents no coronary disease and three represents coronaries blocked by severe disease, the average score of the 32 hemochromatosis, or iron overload, patients (17 men, 15 women) was 0.50. That compares to an average score of 0.92 for 32 age- and sex-matched "controls" without iron overload.

So people with iron overload "tended to have less -- certainly not more -- coronary disease," Miller says.

Some iron overload patients do have "infiltration" of iron into the heart muscle, which may result in a condition called cardiomyopathy that weakens the heart, Miller says. "But that's a different process from hardening of the coronary arteries." This is the first study examining the severity of coronary artery disease in individuals with iron overload, he adds.

Miller and Hutchins both graded the coronary arteriograms "blindly." Test reports were mixed so neither researcher knew whether a particular arteriogram was from an iron-overload patient or a "control."

When they analyzed the autopsy reports for the 33 iron overload patients without post-mortem coronary arteriograms, they found coronary artery disease was "a rare pathologic finding" in that group, too. The researchers studied all available pathological data on these patients including microscopic examinations and physicians' detailed comments, Miller notes.

To verify the findings of iron overload noted in the autopsy reports, Hutchins and Miller also looked at slides of tissue from the spleen, pancreas and liver from both groups. They found iron deposits in tissues from several members of the control group, so those patients were dropped from the study. The same was done with several members of the hemochromatosis group who did not appear to have iron deposits.

Overall, the autopsy reports were "very accurate," Miller says.

Cholesterol levels were available for 33 of 64 more recently autopsied patients, including iron overload cases and controls. "Our data suggest if you don't have elevated cholesterol levels, the link is weak between iron levels and heart disease," Miller says. Only four patients with iron overload had cholesterols over 240 mg/dl. The worst case was an iron overload

patient with a cholesterol of 329 mg/dl, he says, "and that patient had severe coronary disease."

For the iron-overload group, the average cholesterol level was in the 160 to 170 mg/dl range, "which is desirable because it is well below the level of the average American," Miller notes.

In their report, the researchers conclude: "These results indicate that iron overload patients are not at increased risk for coronary artery disease (CAD) and suggest that other factors may account for the enhanced CAD rate previously reported."

In contrast to that previous report by a group of Finnish scientists led by Jukka T. Salonen, M.D., Ph.D., at the University of Kuopio, Miller says: "Iron did not seem to be an independent risk factor in our study."

In explaining differences between the two findings, Miller points out that the people in the Finnish study who had the highest risk of CAD were the ones who had high cholesterol levels as well as elevated iron levels.

People who are anemic and need iron supplements should not be afraid to take them, the Baltimore scientist emphasizes -- unless they have above-average levels of LDL, the so-called bad form of cholesterol.

The theory is that "oxidized" forms of LDL-cholesterol harm the walls of the coronaries and other arteries, eventually leading to atherosclerosis, or hardening and narrowing of the arteries. But Finnish researchers are having a difficult time ironing out their differences on this issue.

At the same AHA conference this week, one Finnish team -- Rainer Rauramaa and his colleagues at the Kuopio Research Institute of Exercise Medicine -- reported their "data do not support the hypothesis that iron is associated with prevalent atherosclerosis."

The researchers complain that several large-scale population studies with negative results on the role of iron in the development of coronary heart disease "have not gained any significant attention at all" compared to the widespread publicity about the study by their neighbors, the University of Kuopio team.

And a second team of Finnish scientists, Matti Manttari and his colleagues at Helsinki University and the National Public Health Institute, Helsinki, reported that it's not the iron, but the iron-carrying molecule, ceruloplasmin, that may be linked with atherosclerosis.

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**MEDIA ADVISORY: Dr. Miller's office telephone number is (410) 328-6299.  
(Please do not publish this telephone number.)**