However, on certain points the analysis and discussion are incomplete.

The abstract version of the study should have been cited, noting that the conclusions drawn in the abstract differed substantially from those in the full paper.

The abstract did not include data on the significant association of heme iron intake with myocardial infarction. Only the negative evidence based on total iron intake was presented. The peer-reviewed version included data on total and heme iron intake and drew conclusions that strongly support the iron theory. Documenting omission of the positive findings is particularly important in this case because the abstract was given prominence as the subject of a news release from the American Heart Association.5 Despite allusions to the heme iron intake data in the news release, the published abstract was widely interpreted as evidence against the iron theory. Publishing only the negative evidence and omitting the interesting and important positive evidence have added confusion to the debate and may have inappropriately discouraged research on iron and heart disease.

The iron theory, in focusing on protective effects of iron depletion, does not stipulate a necessary relation between heart disease and dietary iron. The key hypothesis concerns the relation between heart disease and iron in the body, not necessarily iron in the diet. Dietary iron intake is obviously the source of stored iron in the body. However, stored iron may be absent in the face of very high levels of intake if there is regular blood loss, eg from menstruation, frequent blood donation, or daily use of aspirin.

The authors note correctly that “oxidative stress can free iron from ferritin.”1 However, they miss the point of the iron theory2,3 in suggesting that an oxidative stress may be required for stored iron to have any adverse effect. Free iron cannot be released from ferritin if there is no ferritin present. The absence of ferritin iron is inherently benign. In its absence, in a clinical state of iron depletion, even severe oxidative stresses cannot mobilize free iron from storage. The authors fail to cite evidence from animal experiments suggesting that removal of stored iron has a potent antioxidant effect in vivo.5,10 Free iron liberated from stored iron may be required for many of the adverse effects of an oxidative stress.

The lack of association of heme iron intake with risk of coronary bypass surgery (CABG) does not invalidates the association of heme iron intake with myocardial infarction. As a “coronary event,” the CABG must be carefully distinguished from spontaneous myocardial infarction. Indications for CABG are defined by practitioner consensus, whereas myocardial infarctions are produced by still incompletely defined pathologic processes. There are as yet no reliable criteria for identifying individual asymptomatic subjects who will go on to experience myocardial infarction. Lack of association of heme iron intake with CABG also does not exclude an important role for iron in atherogenesis. Much more research on the specific role of iron in atherogenesis is needed. Very little is known about the kinetics of iron-catalyzed low density lipoprotein (LDL) oxidation in vivo. It may be that very small quantities of stored iron are enough for substantial promotion of LDL oxidation in vivo, ie that nearly complete iron depletion is required for LDL protection. There are also potential mechanisms of iron-promoted atherogenesis that may not directly involve mediation by free radicals. Monocyte-macrophage proliferation in atherosclerotic lesions could be regulated in part by stored iron level. This cell type is of central importance in atherogenesis and also in iron metabolism. Perhaps very small amounts of stored iron are enough for maximal stimulation of monocyte-macrophage proliferation within atherosclerotic plaques.

References

Identification of Coronary Artery Stenoses and Poststenotic Blood Flow Patterns Using a Miniature High-Frequency Epicardial Transducer

To the Editor:

We read with interest the article of Kenny and Shapiro on the identification of coronary artery stenoses and poststenotic blood flow patterns using a miniature high frequency epicardial transducer.1 We were puzzled by the described finding of systolic flow reversal in the poststenotic segment occurring in the absence of retrograde collateral filling of the vessel. Coronary flow velocity patterns measured both by transesophageal echocardiography and by a Doppler flow velocity guidewire do not generally demonstrate systolic flow reversal in arteries that are not supplied by mature or acutely-recruited collaterals.2 Six of the 9 patients with systolic flow reversal had angiographic evidence of collaterals. However, persistent simultaneous antegrade diastolic flow would be unusual for collateral flow patterns.2 The explanation of systolic flow reversal in the absence of hyperdynamic systolic myocardial function, such as hypertrophic cardiomyopathy or aortic stenosis, is unclear.

The concept of an intramyocardial pump as an explanation for systolic flow reversal raised by the authors does not explain why previous observations have shown that diastolic flow is initially more limited by significant narrowing of the vessel than is systolic flow.3,4 Progressive coronary narrowing produces a continuous spectrum of diminishing flow velocity first with a decrease in diastolic flow altering the normally diastolic-predominant flow pattern and then with more hemodynamically severe stenoses, with reductions in both diastolic and systolic flow velocity integrals. One could speculate that systolic flow reversal might be due to transducer positioning with potential imaging of septal artery flow during systole.

The subtotal occlusion in patient 14 with normal proximal velocities had even higher postocclusion velocities, suggesting that the distal velocity measurement was made in a poststenotic segment immediately adjacent to the zone of translesional jet flow supplied by collateral input. A higher distal velocity could be explained by diffuse distal artery disease diminishing the lumen and increasing flow velocity, a finding evident on two-dimensional echocardiographic imaging.

Six patients (1, 10, 13, 15, 17, and 20) had distal diastolic flow velocity exceeding proximal velocity by 37-191%. Without knowl-
edge of the location or diameter of the vessel segment under study, these distal velocity findings are not consistent with previous velocity data for normal or stenosed arteries in awake patients.\textsuperscript{5,6} It is likely that the velocity recordings were obtained in diffusely diseased distal segments (Fig 4), but imaging results of the segments under study were not reported. High distal velocity data may have been produced by compression of the distal artery by manipulation of the transducer on the surface of the vessel. Neither transducer artifact nor distal disease was discussed as an explanation.

The designation of lesion severity based on a 70% angiographic diameter stenosis by visual estimation may not reflect the clinical or hemodynamic severity of the narrowing. Of note, several severe stenoses (patients 4, 8, and 9) had nearly equal proximal and distal flow velocity, which in branching arteries suggests minimal translesional pressure gradients independent of angiographic severity.\textsuperscript{6}

Finally, we take issue with the discussed limitations of a Doppler flowwire for poststenotic velocity measurements. In our experience, the Doppler guidewire tip only rarely (<10%) cannot be directed away from the wall to sample the central velocity stream and adequately characterize distal flow velocity. It is true that tortuous coronary segments require more manipulation than straight segments, but this has not been a major technical limitation. This technique does not have the potential to induce epicardial vessel change by the pressure of the operator’s hand assessing the surface morphology with imaging and Doppler at the same time.

Despite these reservations, we commend the investigators on a unique and detailed approach to study coronary flow velocity as an adjunctive intraoperative assessment of lesion severity.

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