Iron, platelet function, and coronary heart disease: a possible link?

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First, Cosio and colleagues are confused by our use of the terminology "early activation." Surely, the term itself is not in question, but rather its electrophysiological implications. As we stated in our "Methods," and as is always used in the electrophysiological literature, early activation implies the onset of local endocardial electrical activity before the onset of the associated surface ECG parameter, in this case the F or P wave. We agree with Cosio that progressively early activation may be seen as the mapping catheter is moved progressively more proximal to the area of slow conduction in the posterior right atrium. However, in areas where we observed exact (concealed) entrainment maps with a short stimulus-to-P-wave interval, presumably at the exit from the area of slow conduction, we consistently observed discrete or split electrograms with activation −20 to −50 msec before onset of surface ECG flutter wave. These observations are similar to those in studies of reentrant ventricular tachycardia involving an area of slow conduction in which endocardial electrograms from the area of slow conduction or the exit site from the area of slow conduction typically precede the onset of the QRS on the surface ECG.[2,3] In contrast, if human type 1 atrial flutter were caused by functional reentry without an anatomically determined area of slow conduction (as is probably the case in type 2 atrial flutter), our assertions would probably not be valid. In this situation, progressively "early activation" would indeed be seen around the reentry circuit, and in fact, it might even be difficult to determine F or P wave onset on the surface ECG. Thus, although we may not have made it entirely clear in our "Methods" and "Discussion" sections of the article, we meant to imply that electrograms recorded from what we believe to be the exit from the area of slow conduction typically demonstrated "early activation" relative to F- or P-wave onset on the surface ECG.

Another point of concern related to our pacing entrainment data. Cosio et al state that pacing from a large area may "reproduce" P-wave morphology. We agree that although similarities in entrained and flutter P-wave morphology may occur over a large area, an exact 12-lead P-wave match was observed in only a very discrete area in our patients. Otherwise, subtle to very obvious P-wave fusion was observed when pacing entrainment was performed at any significant distance proximal or distal to the area of slow conduction. Using the 4-mm tip electrode as a guide, this area in which concealed entrainment was observed is probably not more than 1 to 2 cm^2 in all cases. Furthermore, we disagree with Cosio et al regarding their comments on stimulus-to-P-wave interval. Although the inferior ECG leads II, III, and aVF were certainly the best leads to see P-wave onset, other leads, including V_1, showed similar stimulus-to-P-wave intervals. Because of the magnification of the figures in the printed article, this may not be entirely clear. However, in some leads that typically record isoelectric P waves in type 1 atrial flutter (eg, lead I), measuring stimulus-to-P-wave interval is not possible. Thus, we recommend that this measurement be performed in the inferior ECG leads.

With regard to the anatomic versus standard fluoroscopic and surgical description of atrial structures, we prefer to continue to use our descriptions because they are well established in the electrophysiological literature, particularly that describing radiofrequency ablation techniques for cardiac arrhythmias.

Last, the authors suggest that a simpler anatomic approach might be just as successful as a mapping and entrainment guided approach. This may be true in some cases, but there may also be some disadvantages to the use of just an anatomic approach. Although most patients required multiple radiofrequency energy applications in our series, retrospective review of the data clearly demonstrated that successful sites had the best entrainment pace map P-wave match. Thus, although a number of lesions were ineffective, a single discrete lesion was eventually effective in each case, and the number of lesions was quite variable. Since our first report,[1] we have treated an additional seven patients in whom the overall success rate was similar (about 85%), with follow-up up to 16 months. In three of these additional seven patients, we observed exact entrainment pace maps, early activation, and short stimulus-to-P-wave interval only inside the coronary sinus ostium in which ablation was successful. In two other patients, two distinct morphologies of atrial flutter required separate discrete lesions just inferior and just posterior to the coronary sinus ostium for successful ablation. Therefore, in these five patients, a strictly anatomically guided approach to ablation of the "isthmus" probably would not have been effective. An additional concern over the use of a strictly anatomic approach is that, if it is initially unsuccessful, the associated edema and tissue damage may make a subsequent entrainment and map guided approach difficult if not impossible.

We are pleased that Cosio et al have had overall success similar to that reported in our study, as have other centers in small numbers of patients. Therefore, we continue to be optimistic that radiofrequency ablation of isolated type 1 atrial flutter will be a useful alternative to drug therapy in many patients, whichever methodological approach is used. We wish to thank Cosio et al for their thoughtful comments.

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Iron, Platelet Function, and Coronary Heart Disease: A Possible Link?

Salonen et al[1] have recently reported an interesting study in which they suggest that iron may be an independent predictor of myocardial infarction (MI) in a Finnish population. They have followed up 1931 randomly selected healthy subjects for an average of 3 years and recorded the acute ischemic episodes that occurred during this period. The result of this study was that subjects with high serum levels of ferritin are at higher risk of MI. In particular, patients with serum ferritin ≥200 μg/L have a 2.2-fold risk factor–adjusted higher risk of acute MI compared with subjects with lower ferritin levels. They hypothesized that such association may reflect the interaction between iron, oxygen free radicals, and fatty acids, which leads to the formation of lipid peroxides.

Whereas an increased lipid peroxidation mediated by iron stores may accelerate atherosclerosis progression, this could not be the mechanism eventually involved in the occurrence of MI, which, in fact, is due to a thrombotic complication of atherosclerotic coronary artery disease. The increased rate of MI in patients with high serum levels of ferritin could, in fact, be due to a direct interaction between iron and blood cell components, in particular, platelets, which play a pivotal role in acute coronary syndromes. Such a role of platelets is well documented by clinical trials of antiplatelet drugs in unstable angina and MI.[2-4]

We have demonstrated recently that platelets are activated through a mechanism involving oxygen free radicals.[5] These radicals have been further characterized by ESR spectroscopy as hydroxyl or "cripto-hydroxyl" radicals generated by a Fenton-like reaction catalyzed by iron. Both free iron or redox-active iron bound to low molecular weight chelators such as EDTA or iron contained in metal proteins (such as hemoglobin) are effective in inducing platelet activation, as documented by an increased aggregation and serotonin release. Thromboxane A_2 is likely to play an

important role in such activation because the effects of iron on platelets were abolished by blocking the prostaglandin G/H-synthase enzyme by aspirin. Taken together, these data may suggest that high levels of iron stores could increase the risk of MI by favoring platelet activation in the setting of plaque fissuring in a major coronary artery. This hypothesis is currently being investigated in vivo by studying platelet function in relation to the levels of serum ferritin.

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Reply

Balsano and coworkers present a hypothetical claim in their letter: "Whereas an increased lipid peroxidation mediated by iron stores may accelerate atherosclerosis progression, this could not be the mechanism eventually involved in the occurrence of myocardial infarction, which, in fact, is due to a thrombotic complication of atherosclerotic coronary artery disease." In our understanding, the current consensus concerning the pathophysiology of myocardial infarction is that both atherosclerotic and thrombotic phenomena may contribute to the acute event, but not both of them in all cases.[1] Fatal acute myocardial infarctions (AMIs) have been described in patients with no signs of either atherosclerosis or thrombosis in the autopsy. In these cases, AMI has been thought to have been due to "coronary spasm" or serious arrhythmia. Also, AMI may occur without any coronary thrombosis.[1] As coronary atherosclerosis is present in the majority of patients with AMI, in our view, pathophysiological mechanisms contributing to atherogenesis are also important in the etiology of AMI. On the basis of the evidence concerning the role of lipid peroxidation[2,3] in atherogenesis, these include factors promoting the oxidation of lipids, such as redox-active iron.

The finding by Balsano and coworkers concerning the role of iron-derived oxygen free radicals in the activation of platelets is an important additional contribution to the comprehensive understanding of the mechanisms through which iron overload and high exposure to redox-active iron promote the development of atherosclerosis and coronary heart disease. Activated platelets play an important role (besides in thrombogenesis) in atherogenesis.[3,4] However, their observation does not in any way exclude the possibility of other mechanisms.

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Interposed Abdominal Compression–Cardiopulmonary Resuscitation

In their recently published article, Sack et al[1] reported a prospective study of the outcome in patients suffering from asystole or electromechanical dissociation who received interposed abdominal compression–cardiopulmonary resuscitation (IAC-CPR). They conclude that the addition of IAC-CPR improves short-term outcome for traditionally difficult rhythms. I write to bring attention to the problem of airway management used in IAC-CPR.

There is potential for confusion among several terms: emesis, regurgitation, and aspiration. The first is a synonym for vomiting, an act that results in the forceful expulsion of gastric contents. Regurgitation refers to the gentler, passive flow of gastric material up the esophagus into the pharynx. Aspiration is said to have occurred when the vomited or regurgitated contents of the stomach (or other material) pass the glottis and enter the trachea.

Sack and coworkers state that 8 of 67 patients in the IAC-CPR group and 8 of 76 in the control suffered emesis before intubation. After intubation, corresponding figures were five for each group. However, they report these data in Table 7, entitled "Complications; Aspiration: Before and After ETT." Thus, the authors fail to make several important distinctions: How many of these patients suffered aspiration, and how many vomited or regurgitated and did not aspirate, either because airway reflexes were intact (unlikely) or because the airway had been protected by intubation with a cuffed endotracheal tube?

An important question is whether the added risk of regurgitation and aspiration outweighs the benefits of IAC. If so, should interposed abdominal compressions be added to chest compressions only after the airway is secured?

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Reply

We appreciate Dr. Salgos' interest in our recently published article reporting improved survival during in-hospital cardiac arrest with interposed abdominal compression–CPR (IAC-CPR).[1] Dr. Salgo is correct in pointing out our use of ambiguous terminology for describing emesis, regurgitation, and aspiration. The end point measured in all patients in the study was visible regurgitation of gastric contents. A patient was considered to experience "emesis" if any gastric material was seen in the oropharynx. Observations were made before and after endotracheal intubation. Therefore, patients described as having experienced emesis included those patients who experienced gastric content regurgitation. It is extremely difficult to determine on clinical grounds whether aspiration has occurred. We do not