Iron, unstable plaque and magnetic resonance imaging

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The concept of unstable plaque leading to thrombosis in acute coronary syndromes (ACS) is well established. Although there have been significant recent advances in understanding the precursors to plaque instability, the morphology, composition and hemodynamic severity of coronary plaques leading to ACS remain to be completely understood. In this setting the pathogenetic role of iron is often not considered.

Iron is an essential nutrient in humans, and states of both iron deficiency and iron excess result in deviation from optimal health. Iron is a fundamental cofactor for several enzymes involved in oxidation-reduction reactions due to its ability to exist in two ionic forms: ferrous (Fe⁺²) and ferric (Fe⁺³) iron. The ability of iron to be converted between these oxidation states through the acceptance or donation of an electron is a key factor in allowing it to perform a range of biological functions. Although the presence of iron in the body is essential in the context of oxygen transport, it is also important to note the potentially damaging consequences that result from interactions between these two molecular forms.

In late adolescence, men begin a steady accumulation of storage iron with age, but women fail to acquire significant iron stores because of their continual loss of iron in menstrual blood, pregnancies and deliveries. An escalation of risk follows initial acquisition of significant stored iron after cessation of menses due to natural menopause or to surgical removal of the uterus and/or the ovaries. The amount of free iron available at sites of oxidative or inflammatory injury appears to be a function of the stored iron level. Removal of stored iron from the body by phlebotomy, systemic iron chelation treatment or dietary iron restriction has been shown to decrease the amount of iron deposition within atherosclerotic lesions in animal studies. Also epidemiological observations suggest a role of iron depletion in cardiovascular protection: (i) lower stored iron level mediated by cyanosis-induced hypoxia may explain why cyanotic patients with congenital heart disease might be protected from atherosclerosis; (ii) the protection against ischemic cardiovascular disease in individuals with impaired hemostasis might be related to the decrease of stored tissue iron caused by recurrent bleeding.

On the other hand, a wealth of evidence has established that intraplaque hemorrhage (IPH) represents a key determinant of atherosclerosis progression and plaque destabilization. The storage and processing of iron from erythrophagocytosis by macrophages within plaque appear to play a key role in plaque progression. Accordingly, it has been demonstrated that erythrocytes induce plaque vulnerability in a dose-dependent manner in a rabbit model of IPH. In this setting, heme catabolism represents a key function in mobilizing macrophage iron derived from ingested erythrocytes. Because IPH induces monocyte recruitment, how monocytes respond to hemoglobin is critical in determining the outcome of IPH. Heme-oxygenase (HO) is the rate-limiting enzyme in the catabolism of heme. HO catalyzes heme degradation to iron, carbon monoxide and biliverdin. HO-1 is the inducible isoform of HO that plays an important role as an antioxidant and anti-inflammatory molecule. It has been found that the effect of HO-1 on iron...
homeostasis within macrophages may represent a new tool to prevent foam cell formation and atherosclerotic lesion progression.\(^6\) Furthermore, hepcidin, the key hormone in iron balance and iron recycling, has been recently confirmed to represent a positive regulator of atherosclerotic plaque destabilization via regulating iron homeostasis in macrophages.\(^9\)

Regarding imaging techniques, magnetic resonance imaging (MRI), beyond its enhanced ability to characterize soft tissues when compared with other imaging modalities, is uniquely suited to measure iron in tissues. MRI represents an established, high-resolution tool for \textit{in vivo} imaging of the carotid arteries and atherosclerotic plaque using multicontrast signal-based techniques such as T1-weighted, T2-weighted, proton density and time-of-flight imaging. In particular, the parameter T2* (T two star), which measures tissue magnetic susceptibility, has been historically used to quantify hepatic and myocardial iron. Indeed, in carotid atherosclerosis disease, it has been found that intraplaque T2* quantification reflects microhemorrhage and iron deposition, with more abnormal T2* found in patients with symptom producing plaques.\(^10\)

Future studies should be conducted to better define the role of iron in plaque destabilization. Moreover, the noninvasive nature of MRI and the intrinsic signal of iron that allows MRI-based detection without exogenous contrast administration make MRI an appealing approach to further elucidate iron’s role in human atherogenesis and plaque progression.

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\textbf{References}