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EDITORIAL COMMENT

Personalized Medicine in the Prevention of Reperfusion Injury?*

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Significant advances have been made in reinitiating perfusion after myocardial obstruction to salvage myocardial tissue; however, it is apparent that reperfusion itself can induce myocardial injury. The mechanism for this reperfusion injury has been widely investigated both in preclinical animal models and in man, with considerable evidence pointing toward a role of oxidative injury and inflammatory cytokines mediating this reperfusion injury. At present, there is no effective therapy that has been shown to reduce reperfusion therapy in man.

One proposed mechanism for reperfusion injury that has been suggested may be related to the haptoglobin (Hp) phenotype. The Hp gene has 2 classes of alleles, 1 and 2, defined by the absence or presence respectively of a 1.7-kb direct repeat resulting in duplication of exons 3 and 4 of the Hp 1 allele (1). Individuals homozygous for the Hp 2 allele are said to have the Hp 2-2 genotype (approximately 40% of the population in the United States and Europe) (1). There is a 1:1 correspondence between the Hp genotype and Hp phenotype, with the Hp genotype being determined directly from the deoxyribonucleic acid by polymerase chain reaction, whereas the Hp phenotype is determined by examining the Hp protein (by enzyme-linked immunosorbent assay, high-performance liquid chromatography, or electrophoresis methods) (2,3).

The Hp protein products generated from the Hp 1 or Hp 2 alleles differ markedly in their ability to modulate the oxidative damage mediated by extracorpuscular hemoglobin (Hb) and in the trafficking of Hb (4). The Hp protein binds with exceptionally high affinity to Hb (K_D 10^{-15}), but the binding of Hp 2-2 does not completely inhibit the ability of Hb to mediate oxidative reactions via Fenton type reactions and is quite inferior to the Hp 1-1 protein in this antioxidant capacity (5). The clearance of free or extracorpuscular Hb is regulated by the Hp protein, which directs the removal of the Hp-Hb complex via the scavenger receptor CD163 present on monocyte macrophages. The Hp genotype has been shown to regulate the clearance of Hb both in vitro and in transgenic mice with the Hp 2-2 genotype associated with an approximately 5-fold longer half-life for extracorpuscular Hb than the Hp 1-1 genotype (6). Because reperfusion injury is associated with hemorrhage and hemolysis, the potential role of Hp in providing protection against reperfusion injury becomes apparent. Blum et al. (7) have demonstrated in a murine ischemia reperfusion model that the Hp 2 genotype was associated with greater injury than the Hp 1 genotype. Furthermore, underscoring the importance of oxidative stress in this model of reperfusion injury mediated by the Hp type antioxidant therapy was able to remarkably reduce this injury (7).

In this issue of *iJACC*, Pontone et al. (8) report on the association of reperfusion injury in man with the Hp phenotype as assessed using cardiac magnetic resonance imaging. Consistent with the preclinical and animal models, the Hp 2-2 genotype was found to be associated with increased injury manifest by more frequent microvascular obstructions (MVO) (8).

MVO denotes profound myocardial damage whereby conventional low-molecular-weight gadolinium-based contrast agents cannot enter the infarcted myocardium even 10 min after contrast administration. As such, MVO appears as utterly dark areas within the otherwise enhanced myocardial infarction on late gadolinium enhancement cardiac

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magnetic resonance images. Readily identifiable MVO on late gadolinium enhancement images yields high intraobserver and interobserver intraclass correlations (>0.8) (9).

The ominous nature of MVO underscores it biologic importance. Several investigators have demonstrated that the presence and extent of MVO associates with worse remodeling (10) and poor outcomes in medium to large cohorts, with ST-segment elevation myocardial infarction (9–12) providing incremental prognostic information beyond echocardiography and conventional risk scores (9,11–13).

The results of this study linking Hp phenotype with MVO are important for several reasons. First, they suggest that it may be possible to predict which individuals will have more reperfusion injury before initiating reperfusion on the basis of a readily determined biomarker. Second, they suggest that an important mediator of this oxidative injury may be extracorpuscular hemoglobin; accordingly, therapies designed to reduce injury from Hb may be beneficial. Finally, they suggest a personalized approach to prevent reperfusion injury in which the therapy would be determined by the Hp type of the patient.

There are considerable data supporting the use of antioxidant therapy in Hp 2-2 individuals to improve cardiac outcomes, and a recent meta-analysis has shown a pharmacogenomics interaction between vitamin E and the Hp type on cardiac disease, particularly in the setting of diabetes (14). Of interest, no benefit from vitamin E was found in the non-Hp 2-2 population. This may explain why prior attempts to reduce reperfusion therapy with antioxidant therapy, which was given to all patients regardless of genotype, did not demonstrate any benefit. As proposed by Pontone et al. (8) in this issue of *iJACC*, it may be prudent to try to administer antioxidant therapy in Hp 2-2 individuals before reperfusion therapy. This would require a rapid screen for the Hp type. An example of such a rapid screening test has recently been reported in an enzyme-linked immunosorbent assay format, but additional possible screening tests may be possible depending on the resources available in the medical center.

Personalized medicine, based on administering drugs to a select patient population based on a genetic polymorphism, has received much hype. There is hope that it may yield real clinical benefit; the best way that this can be achieved is if it is based on solid preclinical data including animal models of the polymorphism backed up by human data, as this study appears to suggest. We await further testing of this hypothesis.

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