

EDITORIAL COMMENT

Heart Failure

Not Enough Pump Iron?*

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The intriguing study of Maeder et al. (1) further shifts the focus on anemia in heart failure away from hemoglobin and towards iron. Indeed, the prevalence and potential importance of iron deficiency per se, irrespective of hemoglobin, is a subject of intense interest in heart failure at present (2–6). Because there are no agreed-upon criteria for the diagnosis of iron deficiency, prevalence varies widely (7). However, 1 study, using the “gold standard” of bone marrow iron staining, reported that as many as 73% of patients with advanced heart failure had iron deficiency (8). Using alternative diagnostic criteria, Jankowska et al. (3) recently showed that iron deficiency in patients with heart failure was associated with a significantly worse prognosis, independent of anemia.

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The current study adds further evidence to an emerging picture that paints an important role for iron deficiency in heart failure (1). The key, new findings of Maeder et al. are the demonstration of reduced iron content and transferrin receptor 1 (TfR1) expression in the myocardium of patients with heart failure, compared with controls, and the finding that TfR1 expression is regulated, experimentally, by beta adrenoceptor agonists and aldosterone (although not natriuretic peptides). The first of these findings has resonance with experimental studies in animals that showed that induction of iron deficiency leads to myocardial hypertrophy and, eventually, the devel-

opment of systolic dysfunction (4,9). Catecholamines seem to play a role in the changes in these experimental models, linking to the second finding of Maeder et al. (1). It is, therefore, tempting to speculate that myocardial iron depletion, perhaps caused by neurohumorally mediated TfR1 down-regulation, contributes to decline in systolic function and clinical progression in patients with heart failure (10). This is pathophysiologically plausible, given the crucial role that iron plays in cellular function in general and oxidative metabolism in particular, especially in metabolically active tissue (4). Although attractive, this hypothesis needs further testing. The number of individuals studied by Maeder et al. (1) was small (myocardial samples were obtained from 6 explanted failing hearts and 5 unused donor hearts). The comparison was extreme, that is, healthy heart muscle was compared with that from patients with end-stage heart failure undergoing transplantation. The subjects studied were also far from typical—the average patient age was 46 years, and the donor hearts were from even younger individuals. The experimental studies of TfR1 regulation were also conducted in cardiomyocytes from young rats and with high concentrations of adrenoceptor agonists and aldosterone.

So, what could be done to test this intriguing new hypothesis? Three thoughts come to mind. First, it may be possible to adapt new magnetic resonance imaging techniques, currently used to identify myocardial overload, to detect iron depletion (11). This would allow noninvasive verification of the current findings. Second, the potential role of beta-adrenoceptors and aldosterone in mediating myocardial iron deficiency by down-regulating TfR1 could be tested with the same imaging approach, if viable, using beta-blockers and aldosterone antagonists. Last, the effect of iron replenishment on ventricular structure and function could be examined. With respect to the latter idea, there is already preliminary evidence that iron supplementation of deficient patients may improve exercise performance, New York Heart Association functional class, and a number of patient-reported outcomes (12).

Doubtless this story will turn out to be more complex than outlined. Iron deficiency and anemia are inextricably linked, and dissecting out the pathophysiological role (if any) played by iron deficiency versus anemia (and diminished oxygen delivery) per se is difficult (7). The contribution of regulators of iron metabolism, such as hepcidin and hypoxia inducible factor, which may be present in the myocardium and have a variety of actions, is currently uncertain (9,13). Another of these, erythropoietin, is being tested as a treatment in a trial of anemia correction in heart failure, which is presently underway (14).

One thing is clear. The novel and interesting findings of Maeder et al. (1) must now make cardiologists think about the possibility that iron depletion, as well as iron overload, might lead to myocardial dysfunction (15).

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