HEART FAILURE (HF) is a major public health problem worldwide. HF is a syndrome arising from multiple causes that will affect one in five adults in their lifetime. Despite the progress that has been made in the treatment of chronic HF, the overall morbidity and mortality remain high (8). Therefore, it is imperative that there is a continued push to more fully understand the molecular mechanisms responsible for this disease to discover and develop novel therapies. Among the multiple characteristics of chronic HF, anemia, defined by the World Health Organization criteria as a hemoglobin (Hb) concentration of <13 g/dl in adult men and <12 g/dl in adult women, is found in 30% to 40% of cases and is an independent risk factor for more severe HF (1, 2, 12, 17).

When compared with HF patients with normal Hb levels, the presence of anemia is associated with worsened clinical symptoms, more severe systolic and diastolic dysfunction, and a significant increase in mortality in patients with advanced HF (4, 6, 7, 17). Moreover, these patients have higher brain natriuretic peptide levels, increased extracellular and plasma volume, and more rapid deterioration of renal function. It has been shown that chronic untreated anemia can result in increased cardiac output that eventually can lead to ventricular dilation, increased left ventricular (LV) mass, and the development of LV hypertrophy, which represent cardiac remodeling parameters that are strong predictors of morbidity and mortality (12). Understanding how chronic anemia leads to LV remodeling and poorer outcomes in HF is essential to improve how we may treat these large number of patients with HF.

Naito and colleagues (12a) report an animal model of chronic anemia that leads initially to an adaptive phase of preserved cardiac function despite LV remodeling followed over time by maladaptation and severe LV dysfunction. The compensatory phase followed by decompensation appears to correlate with the dynamic regulation of serum erythropoietin (EPO) levels and cardiac EPO signaling. This study underscores the significance of cardiac EPO-EPO receptor (EPO-R) signaling as a cardioprotective axis.

EPO, a hematopoietic cytokine that is primarily synthesized in kidney peritubular cells in response to hypoxia, has long been used as a clinical treatment for conditions of low Hb. The physiological effects of EPO in hematopoietic cells are mediated through its interaction with its specific cellular receptor, EPO-R, a member of the type I superfamily of single-transmembrane cytokine receptors (3, 9). Recently, data have accumulated demonstrating that the EPO-R is present in a variety of other tissues outside the blood, including cardiomyocytes, suggesting the potential roles of EPO signaling beyond hematopoiesis and the treatment of anemia (20). Recombinant human EPO administration has been shown to exert a broad tissue-protective effect in a variety of experimental models. In the cardiovascular system, EPO has been shown to exert marked myocardial protective effects against ischemia-reperfusion injury via a reduction of LV infarct size and a significantly decreased apoptotic cell death of cardiomyocytes, which leads to an enhanced recovery of LV function (5, 16). Mechanistically, studies have shown that EPO-EPO-R signaling can stimulate the JAK/STAT, MAPK, and phosphatidylinositol 3-kinase/Akt signaling pathways in cardiac cells, much like the signaling in hematopoietic cells (13, 14). Cardioprotection after ischemic injury characterized by increased angiogenesis in the heart has also been found using darbepoetin-α, a longer-acting synthetic EPO analog (11, 18). In apparent support of the cardioprotective actions of EPO and analogs, recent clinical trials have shown that in anemic patients with HF, EPO treatment increases and maintains Hb and LV ejection fraction with improved quality-of-life scores and exercise duration (10, 15, 19). However, the mechanism of these beneficial effects of EPO in patients with anemic HF has not been fully understood or clarified.

In the study by Naito et al. (12a), important mechanisms behind the adaptive and maladaptive responses of the heart to a long-term anemia induced by iron deficiency have been uncovered. First, they demonstrate in rats that iron deficiency anemia (IDA) leads to cardiac hypertrophy at 12 wk with a maintained cardiac output. However, after 20 wk of IDA, serial echocardiographic measurements revealed significant cardiac dysfunction characterized at the end of the study by an increase in the LV weight-to-tibia length ratio and the lung wet weight-to-lung dry weight ratio. Moreover, at a molecular level, atrial natriuretic peptide, brain natriuretic peptide, and collagen type 3 gene expressions were increased, consistent with the myocardial interstitial fibrosis that was evident in IDA rats. Interestingly, circulating levels of EPO were inversely correlated with these phenotypic findings, with upregulation at 12 wk and a significant decrease at 20 wk, suggesting a change in EPO-EPO-R signaling in the late-stage HF induced by IDA.

This study revealed some potentially important mechanistic findings implicating STAT3 activation as a culprit in IDA-induced maladaptation. Of note, serum EPO levels and the phosphorylation of STAT3 peaked at 12 wk and subsequently decreased at 20 wk, raising the possibility that a compensatory and decompensatory EPO-EPO-R signaling mechanism may exist in the hearts of rats with chronic IDA (12a). Consistent with this, a previous study has showed that activated (i.e., phosphorylated) STAT3 can occur in cardiac cells stimulated with EPO (14). Importantly, to further explore whether the preservation of increased EPO levels is associated with adaptive cardiac remodeling, Naito et al. (12a) examined the cardiac effects of EPO therapy on rats after they had been on an iron-deficient diet for 12 wk. EPO administration attenuated the downregulation of cardiac STAT3 phosphorylation and
prevented cardiac dysfunction in the IDA group. Meanwhile, blood Hb and systolic blood pressure were not altered in the IDA group receiving EPO. Increasing EPO levels in these rats clearly prevented the transition from adaptive cardiac hyper trophy to maladaptive LV remodeling and HF even with sustained IDA. Accordingly, the study implicates STAT3 activation to be critical for the EPO-dependent maintenance of LV function despite IDA.

Overall, this study underscores the importance of maintaining EPO levels in HF patients and may open up a new therapeutic window to use this cardioprotective cytokine more frequently, even in patients without anemia. Of course, further studies, especially in larger animals and different models of HF, are warranted since EPO can increase the risk of thrombotic events. Nevertheless, Naito et al. (12a) have shed new light on this interesting field.

REFERENCES