Erythropoietin and ventricular remodelling: a VEGF-dependent neovascularity

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This editorial refers to ‘Vascular endothelial growth factor is crucial for erythropoietin-induced improvement of cardiac function in heart failure’ by B.D. Westenbrink et al., pp. 30–39, this issue.

To uncover novel therapeutics for heart failure (HF), attention has focussed on the biological factors that underlie the transition from an initially adaptive hypertrophic response to a maladaptive state that promotes progressive cardiac dysfunction. The cardiac microvasculature is an important factor in this regard as insufficient capillary growth is thought to be an important contributor to progressive dysfunction and remodelling in HF.¹ Unlike the increased capillary density seen in conditions of physiological cardiac hypertrophy,² reduced microvascular density and fewer capillaries are commonly observed in failing hearts.¹,³–⁶ Microvascular rarefaction in pathological hypertrophy imparts many untoward effects, including myocardial ischaemia due to deficient oxygen supply, inefficient cardiac metabolism, myocyte loss, inflammation, fibrosis, and contractile dysfunction.¹,³–⁶ Changes in myocardial capillary density during myocardial hypertrophy have been linked to the expression of angiogenic factors such as vascular endothelial growth factor (VEGF).⁶ In murine models, pressure overload induces the expression of VEGF and angiopeit,² during the adaptive phase of hypertrophy, whereas blockade of VEGF signalling decreases myocardial neovascularization and accelerates the transition to failure.⁶ Hence, restoration of the cardiac microvasculature theoretically represents a viable strategy to improve cardiac function in HF.

Erythropoietin (EPO) is a growth factor that promotes the differentiation and proliferation of red blood cells from progenitors within the bone marrow in response to hypoxia.⁷ The frequent occurrence of anaemia in patients with HF and the findings that anaemia is an independent predictor of mortality have provided the impetus to test the potential benefit of EPO in HF patients.⁸ However, experimental studies have demonstrated that EPO receptors are also expressed on several non-haematopoietic cell types (including those in the heart) and that EPO imparts erythropoiesis-independent, pro-angiogenic and anti-apoptotic beneficial effects.⁸ In animal models of myocardial infarction, EPO administration has been shown to enhance the mobilization and homing of endothelial progenitor cells (EPCs) to ischaemic myocardium, with associated improvements in capillary density and cardiac function.⁹,¹⁰ These effects on capillary growth also occurred at doses that did not increase haematocrit.¹¹ Similar benefits of EPO on EPCs, neovascularization, and cardiac function were observed in doxorubicin-induced cardiomyopathy.¹² Despite such encouraging preclinical data, thus far the clinical studies of EPO in HF have yielded conflicting results with regard to benefit.⁸ Moreover, clinical trials in patients with chronic kidney disease have shown that completely normalizing haemoglobin levels with EPO increased the risk of cardiovascular and thrombo-embolic events, raising concerns about potential adverse effects of increased blood viscosity and thrombo-embolism with treatment.¹³,¹⁴ A large, multicentre trial using the EPO analogue darbropoietin in subjects with HF is ongoing that should help answer these questions.⁸ Nonetheless, these observations suggest that targeting the erythropoiesis-independent, pro-angiogenic effects of EPO may be a more fruitful therapeutic approach in HF.

Westenbrink et al.¹⁵ have provided important observations regarding EPO-mediated neovascularization in the remodelling heart and the importance of the microvasculature in EPO-mediated improvements in cardiac performance in HF. In a rat model of myocardial infarction, these authors demonstrated that EPO administration augments VEGF expression in the heart predominantly in cardiomyocytes. Using strategies of VEGF neutralization, they further showed that such VEGF expression was required for EPO-induced improvements in neovascularization, myocardial incorporation of EPCs, proliferation of myocardial endothelial cells, and enhancement of cardiac function. Just as important, these beneficial effects were independent of EPO-induced effects on the haematocrit and EPO mobilization. These results extend the prior work by these authors and others, demonstrating that EPO induces VEGF expression, EPO receptor expression and neovascularization in post-ischaemic remodelling myocardium and that improvement in cardiac function occurs in an erythropoiesis-independent manner.⁹–¹² Indeed, the results of the two recent clinical trials examining the effects of EPO in patients with chronic kidney disease suggested that full correction, as

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opposed to partial correction, of anaemia increased the risk of cardiovascular events, underscoring the importance of EPO dosage and the potential detriments of excessive haematopoesis with EPO. In the current study, the authors make a strong case for circumventing the potential adverse effects of increased erythropoiesis by instead therapeutically targeting myocyte-localized EPO signalling.

The authors put forth the notion that there is paracrine control of myocardial angiogenesis by cardiomyocytes in response to EPO. This concept of paracrine effects originating from cardiomyocytes has also been suggested by other investigations examining a variety of signalling pathways in the heart. For example, myocyte-specific expression of the transcription factor GATA4 promotes myocardial angiogenesis by activating VEGF-A gene expression. Also, we have recently shown that myocyte-restricted overexpression of haem oxygenase-1 promotes neovascularization in remodelled myocardium that is probably due to diffusion of its catalytic product carbon monoxide. Interestingly, mice with myocyte-restricted loss of the transcription factor signal transducer and activator of transcription 3 (STAT3) exhibit reduced capillary density and reduced VEGF expression, suggestive of a STAT3-linked, pro-angiogenic paracrine circuit in the heart. Westenbrink et al. have suggested that EPO induces STAT3 phosphorylation in cardiomyocytes, and such a paracrine circuit may be of importance in EPO-induced VEGF expression.

Nonetheless, in order to definitively ascribe a primary role for myocyte paracrine control of angiogenesis in response to EPO, studies would need to be performed in tissue (myocyte or endothelial)-specific knockout models of EPO-receptor and/or VEGF, especially in view of prior studies by this group, demonstrating that EPO also induces VEGF expression in endothelial cells and prior studies by others showing that mice devoid of EPO receptor expression in the vasculature exhibit reduced VEGF expression accompanied by attenuated neovascularization and homing of EPCs. Furthermore, cardiomyocytes express low levels of EPO receptor in comparison with endothelial and fibroblast cells, suggesting that direct effects of EPO on resident myocardial endothelial cells may also be of importance in producing the observed responses. In addition to defining the relative roles of myocyte vs. endothelial cell-specific EPO responses, the molecular mechanisms underlying EPO-induced VEGF upregulation warrant further exploration. EPO has also been shown to activate phosphatidylinositol 3-kinase (PI3K)/Akt signalling during ischaemia/reperfusion, and such activation is thought to be responsible in part for its cardioprotective and anti-apoptotic effects. It would be of great interest to examine the potential crosstalk between STAT-3 (as shown in the current study) and PI3K/Akt pathways in the EPO-mediated upregulation of VEGF, tissue neovascularization, and subsequent improvements in cardiac function. These issues notwithstanding, the study by Westenbrink et al. advances our understanding of the therapeutic potential of EPO in HF and its relationship to VEGF-mediated EPC homing and neovascularization. On the basis of their results, augmentation of endogenous cardiac-localized EPO signalling should be considered and pursued as a potential therapeutic strategy to ameliorate microvascular insufficiency and left ventricular remodelling in HF.

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