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## ERYTHROPOIETIN ATTENUATES CARDIAC DYSFUNCTION IN EXPERIMENTAL SEPSIS VIA ACTIVATION OF THE B-COMMON RECEPTOR

A I Khan,[1] S M Coldewey,[1] N S Patel,[1] M Rogazzo,[2] M Collino,[2] M M Yaqoob,[3] P Radermacher,[4] A Kapoor,[1] C Thiemermann[1] *[1]The Centre of Translational Medicine and Therapeut; [2]Department of Drug Science and Technology, Univers; [3]Department of Nephrology, Barts Health NHS Trust; [4]Division of Pathophysiology and Process Development*

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**Rationale** There is limited evidence that the tissue-protective effects of erythropoietin are mediated by a heterocomplex of the erythropoietin-receptor and the β-common receptor ('tissue-protective receptor'), which is pharmacologically distinct from the 'classical' erythropoietin-receptor homodimer responsible for erythropoiesis. However, the role of the β-common receptor and/or erythropoietin in sepsis-induced cardiac dysfunction (a well known, serious complication of sepsis) is unknown. Here we report for the first time that β-common receptor is essential for the improvements in the impaired systolic contractility afforded by erythropoietin in experimental sepsis.

**Methods and Results** Cardiac function was assessed *in vivo* (echocardiography) and *ex vivo* (Langendorff-perfused heart) in wild-type and β-common receptor knock-out mice, that were subjected to lipopolysaccharide (9 mg/kg; young mice) for 16–18 h or cecal ligation and puncture (aged mice) for 24 h. Mice received erythropoietin (1000 IU/kg) 1 h after lipopolysaccahride or cecal ligation and puncture. Erythropoietin reduced the impaired systolic contractility (*in vivo* and *ex vivo*) caused by endotoxemia/sepsis in young as well as old wild-type mice in a β-common receptor-dependent fashion. Activation by erythropoietin of the β-common receptor also resulted in the activation of well-known survival pathways (Akt and endothelial nitric oxide synthase) and inhibition of pro-inflammatory pathways (glycogen synthase kinase-3β, nuclear factor-κB and interleukin-1β). All the above pleitropic effects of erythropoietin were lost inβ-common receptor knock-out mice.

**Conclusions** Erythropoietin attenuates the impaired systolic contractility associated with sepsis by activation of the β-common receptor, which in turn, results in activation of survival pathways and inhibition of inflammation. Thus, targeting the 'tissue protective receptor' with specific agonists devoid of the erythropoietic effects of erythropoietin may represent a novel approach for the treatment of sepsis-associated cardiac dysfunction. *AIK and SMC contributed equally to this study.