Abstract:

OBJECTIVES: The response to hypoxia is primarily mediated by the transcription factor hypoxia-inducible factor-1 (HIF-1) which leads to the induction of a variety of adaptive gene products including vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS). This study was designed to test the hypothesis that HIF-1 and its target genes would be upregulated in the ventricular myocardium of infants with cyanotic congenital cardiac defects. METHODS: 14 infants with cyanotic (n = 7) or acyanotic cardiac defects (n = 7) were investigated. Samples from the right ventricular myocardium taken immediately after aortic clamping were studied for protein expression and DNA-binding activity. RESULTS: Protein levels of HIF-1alpha were significantly elevated in patients with cyanotic compared to acyanotic congenital heart disease and inversely correlated with the degree of hypoxemia. This response was accompanied by significantly enhanced HIF-1 DNA binding activity. Furthermore, protein levels of VEGF and eNOS were significantly higher in the myocardium of cyanotic than of acyanotic infants. To test the potential involvement of upstream regulatory pathways, activation of MAP kinases was determined. Intramyocardial levels of phosphorylated p38 MAP kinase, but not of ERK1/2 were significantly higher in infants with
cyanotic compared to those with acyanotic congenital heart disease and inversely correlated to hypoxemia. CONCLUSIONS: These findings show that chronic hypoxemia is associated with the induction and stabilization of the transcription factor HIF-1 as well as its target genes VEGF and eNOS in the myocardium of infants with cyanotic cardiac defects. Thus, stabilization of HIF-1 and induction of the adaptive hypoxia response could particularly participate in myocardial remodeling in children with congenital cardiac defects and chronic hypoxemia.